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Grand challenges in arachnid toxinology and biochemistry

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1 Introduction

Venom usage within arachnids is limited to spiders, scorpions, pseudoscorpions, ticks, and maybe even camel spiders if the toxic secretion from their epidermal glands is considered as venom (Aruchami and Sundara Rajulu, 1978; von Reumont et al., 2014). Among the venomous arachnids, spiders and scorpions have received by far the most attention from researchers (von Reumont et al., 2014). Overall, venomous arachnids comprise around 60,000 described extant species, with many more species yet to be characterized (Rein, 2023; World Arachnid Catalog, 2023). Venomous arachnids use their venoms mainly for prey capture and defense (Simone and van der Meijden, 2021; Lüddecke et al., 2022), although some spiders and scorpions use their venom coercively for courtship [males making females more compliant by "sexual bites or stings"; (Sentenska et al., 2020; Olguin-Perez et al., 2021)] and ticks employ venom to facilitate their parasitic lifestyle (Cabezas-Cruz and Valdes, 2014). Arachnid venoms are complex mixtures of metabolites, peptides, proteins and enzymes containing hundreds or even thousands of individual components for each species (Pineda et al., 2020). While arachnids employ these components to provide them with an evolutionary advantage in their respective ecological niche, researchers have realized that the astounding diversity of arachnid venom components can be utilized for the benefit of humanity. For example, applications as therapeutics, bioinsecticides, antiparasitic treatments or for diagnostic purposes are being actively pursued. I therefore hope the realization that arachnids could be beneficial for humans will eventually change their mostly negative public perception as being repulsive and potentially deadly. In the following paragraphs, I will discuss some ongoing and future challenges for toxinological and biochemical research on arachnids which also provides an opportunity to further expand our knowledge on these exciting creatures.

2 Increasing the taxonomic coverage

Of the 91,200 to 114,200 known species of arachnids (Schausperger, 2022), around 60,000 species are venomous, but the venoms of only a couple of hundred species have been studied (Pineda et al., 2018). While initially the focus of toxinological research was on the medically important species, this later changed when species that are not harmful to humans were increasingly explored (Herzig, 2021). However, the major limiting factor that remained was the small size of most arachnids and their correspondingly small venom yields. Research to date has therefore been predominantly focused on larger arachnid species (Herzig et al., 2019; Lüddecke et al., 2019). Technical improvements in experimental methods and sensitivity in the various omics fields (e.g. proteomics, transcriptomics, genomics, metabolomics) and in

spectrometric (e.g. mass spectrometry, nuclear magnetic resonance spectrometry) and chromatographic (high performance liquid chromatography) techniques have now enabled researchers to study much smaller specimens. The most prominent examples are the recent transcriptomic and proteomic studies of the venom of pseudoscorpions (Santibanez-Lopez et al., 2018; Krämer et al., 2019) that are only a few millimeters in length and yield only few nanoliters of venom. The aim for future research in arachnid toxinology and in arachnid science in general (Kuntner, 2022) should therefore be to expand our knowledge of arachnid venoms into unexplored arachnid families or sub-families to provide a wider taxonomic coverage. Broadening our taxonomic knowledge will facilitate phylogenetic reconstructions of venom evolution in arachnids. With experimental techniques continuously improving, the size of arachnids should become less of a limiting factor preventing research on their venoms. The major bottleneck will then shift to sourcing arachnid specimens for research.

While conservation research into arachnids is still in its infancy (Agnarsson, 2023), international agreements like the Nagoya protocol are already in place in many countries that regulate the protection of natural resources, stipulating the need to acquire permits from the respective countries of origin for utilizing their biological sources (Colmenarez et al., 2023). While the idea behind Nagoya is commendable, i.e. to share financial benefits resulting from research with biological sources with the countries of organismal origin, it is already significantly impeding basic research. While I am in complete support of sharing financial benefits with the countries of origin, only a very small fraction of all basic research will ever produce any financial benefits. Furthermore, providing financial benefits to the countries of origin will not automatically ensure that they will be used towards protection of these species for future generations. A main challenge in the field will therefore be to remove unnecessary and unreasonable bureaucratic hurdles for sourcing arachnids for basic and non-profit research. In times of increasing extinction rates for many organisms caused by mostly human-made factors (Cowie et al., 2022), we should make the most of every opportunity to expand our current knowledge on as many arachnid species as possible before some of them become extinct. This also includes the controversial utilization of specimens already available in the pet trade, in particular if captive-bred specimen can be sourced (Herzig et al., 2023). While research always needs to uphold high moral and ethical standards, common sense should not be entirely disregarded. Trade with exotic arachnid pets will exist irrespective of whether scientists use it for sourcing specimens for their research or not and the overall trade numbers are unlikely to significantly change as a consequence. However, any knowledge obtained from this research could potentially provide lasting global benefits to future generations, and not just local short-lived benefits to a few countries of origin.

3 Beyond peptides

The last few decades have seen an immense improvement in our understanding of arachnid venom peptides, with many thousands of peptide toxins already been described (Rodriguez de la Vega et al., 2010; King and Hardy, 2013; Ahmadi et al., 2020). The use of omic methods has further accelerated peptide toxin discovery, with each new venom-gland transcriptome potentially yielding hundreds of new peptide sequences. While there is still much more to discover, particularly in previously neglected arachnid taxa (see Section 2), we should not focus our attention entirely on peptidic venom components. Smaller inorganic and organic components like metabolites, but also larger components like proteins and enzymes, play important ecological roles in the venoms. For example, according to the dual prey inactivation strategy, venom proteins and enzymes are important for the envenomation process by disturbing cellular homeostasis and acting as spreading factors, thereby facilitating the activity of peptide toxins (Kuhn-Nentwig et al., 2019). A wide variety of enzymes and proteins have been reported from scorpion venoms (Delgado-Prudencio et al., 2022), while enzymes and proteins are even dominating pseudoscorpion venoms (Santibanez-Lopez et al., 2018). At the lower end of the size spectrum, small molecules like metabolites have been reported to contribute to the overall activity of arachnid venoms (Wilson et al., 2017; Evans et al., 2020). A holistic approach *would* therefore be desirable for future research to capture the entire chemical diversity of arachnid venoms. This could also include research into whether particular components found in arachnid venoms are actually produced by the arachnid species itself or by microorganisms inhabiting their venom systems (Ul-Hasan et al., 2019; Esmaeilishirazifard et al., 2022; Cabezas-Cruz, 2023). In addition, a holistic approach should take into account that individual venom components often interact with others to potentiate activity and to provide synergistic effects (Lüddecke et al., 2022). Understanding the underlying mechanisms could therefore be advantageous when employing arachnid venom components for the benefit of humans (see Section 5.).

4 Utilizing emerging technologies for arachnid toxinology

With research methodologies continuing to improve and techniques becoming ever more sophisticated, the volume of research data continues to expand. In toxinological research, the increasing use of venom-gland transcriptomics and other omics techniques provides us with massive datasets that require specific bioinformatic tools for their analysis. Making the resulting datasets permanently open accessible for everyone will be one of the key challenges in the field. Ideally, those datasets should be integrated into public databases to enable easy data access for non-specialists that do not have a background in bioinformatics or access to the specific bioinformatic tools. In the field of arachnid toxinology, two specific databases have been available. SCORPION2 focused on scorpion toxins but is no longer available (Tan et al., 2006). ArachnoServer is focused on spider toxins, but only a temporary version with limited functionality is currently available (Pineda et al., 2018). As part of the team involved in the development of ArachnoServer, I am now leading efforts to "refurbish" the application to future-proof it for the coming decades. For the new

ArachnoServer, we aim to expand the focus from spider toxins into toxins from all venomous arachnids. We also plan to add new functionalities to ArachnoServer and are open to suggestions from the research community about specific new functions they would like to be incorporated. One idea is the incorporation of AlphaFold (Jumper et al., 2021) predicted structures for all toxins that do not yet have an experimentally determined three-dimensional structure.

The emergence of AlphaFold and other Artificial Intelligence (AI)-based programs like ChatGPT illustrates another challenge for the field and for science in general, which is how to best implement AI tools to maximize the gain for scientific discovery, and at the same time, eliminate noise and errors. AI tools might provide a solution for managing the ever-increasing volumes of research data created, but the toxinological research community needs to agree on the standards and boundaries for using AI tools. Another challenge with the increasing number of newly discovered arachnid toxins is their nomenclature. While a rational nomenclature has been implemented for peptide toxins (King et al., 2008), a unified nomenclature for all different venom components would be desirable. In addition, the current rational nomenclature has its own limitations, including the susceptibility to frequently occurring taxonomic changes at the genus and species level. Making toxin nomenclature more resistant to taxonomic changes and expanding it to include proteins, enzymes and metabolites will therefore be another key challenge for the entire toxinological community, not just for those working on arachnid venoms. Given that toxins are stored in the respective databases according to their rational names, a more stable and broadly applicable nomenclature is crucial for enabling permanent storage of arachnid toxin data.

Functional genomics techniques such as RNAi and CRISPR are already being used in related areas (Lau et al., 2019; Lüddecke et al., 2023), but haven't yet been employed to increase our understanding of the biology of arachnid venom systems. I'm confident that the full utilization of these techniques for arachnid toxinology will provide significant leaps of knowledge for the entire field. Likewise, the biotechnological production of venom peptides, proteins, and enzymes is another area that requires increased attention from researchers in the future to enable a broad range of possible applications of arachnid venom derived leads.

5 Exploring beneficial aspects of arachnid venoms

Venomous animals and spiders in particular are often associated with a negative public image (Mammola et al., 2020) which is rarely correlated with the danger they pose to humans (Stuber and Nentwig, 2016; Hauke and Herzig, 2017). By further expanding the research on beneficial aspects of arachnid venoms, I hope that studies published in *Frontiers in Arachnid Science* will contribute to establishing a more positive public perception of venomous arachnids. In a recent review, I've identified six potential fields of application for venom compounds, including as pharmacological tools, drug leads, anti-infectives, insecticides, molecular probes and as tools for drug-target identification (Herzig et al., 2020), which all have been examined for arachnid venom peptides in the last few decades. Given the selectivity and potency of arachnid toxins, they have often been used as pharmacological tools for studying the physiological roles of ion channels (Suchyna et al., 2004; Osteen et al., 2016; Lin King et al., 2019) and as potential drug leads for diseases caused by ion channel dysfunctions [as reviewed in (Saez et al., 2010; Smith et al., 2015; Saez and Herzig, 2019; Ahmadi et al., 2020; Mendes et al., 2023)]. The antibacterial and anti-parasitic properties of some arachnid venom components have also been proposed for controlling bacteria and parasites (Saez and Herzig, 2019; Ageitos et al., 2022; Rincon-Cortes et al., 2022; Salimo et al., 2023). Selective modulators of acid-sensing ion channels (ASICs) including those from spider venoms like PcTx1 (Escoubas et al., 2000) and Hi1a (Chassagnon et al., 2017) have been crucial for understanding the physiological and pathophysiological roles of ASIC channels (Cristofori-Armstrong and Rash, 2017) and for establishing ASIC channels as a drug target for treating stroke and heart attack (Chassagnon et al., 2017; Redd et al., 2021). A striking example of using toxins as molecular probes has been realized with fluorescently tagged versions of chlorotoxin, a peptide from venom of the deathstalker scorpion *Leiurus quinquestriatus* (Veiseh et al., 2007). Given that chlorotoxin selectively binds to invasive brain tumors, the attached fluorescent probe provides neurosurgeons with a means of intraoperative visualization of tumor tissues to delineate tumor margins (Veiseh et al., 2007; Akcan et al., 2009). The application of arachnid toxins as bioinsecticides has received a boost with the commercial registration of a spider-venom-derived bioinsecticide on the US market in 2014 by US-based company Vestaron Corporation (Bomgardner, 2017; King, 2019). Dozens of novel insecticidal venom peptides have been discovered in recent decades from spiders and scorpions [reviewed in (Gurevitz et al., 2007; Schwartz et al., 2012; Windley et al., 2012; King and Hardy, 2013; King, 2019; Saez and Herzig, 2019)].

6 Conclusions

Venom research has come a long way from its beginning in the last century of studying only a few medically relevant species. Today's sophisticated methods provide access to venoms from a wide variety of arachnids ranging from the largest tarantulas to species that are just a few millimeters in length. Nevertheless, the field of Arachnid Toxinology and Biochemistry to which this specialty section in *Frontiers in Arachnid Science* is dedicated, has barely scratched the surface and many new and exciting discoveries still lie ahead of us. Key challenges in this field include: 1. Increase of taxonomic coverage, which is not only limited by the size of the respective arachnids, but also by the challenges in sourcing sufficient specimens for research; 2. A holistic approach to arachnid venoms, which comprises the understanding of all individual components and their respective function in the venom, including potential synergistic interactions; 3. Utilizing emerging technologies for arachnid toxinology, with research methodologies and AI becoming ever more sophisticated, we need to utilize both in combination to maximize potential gains; 4. Benefits from arachnid venoms, ranging from pharmacological

tools for studying ion channels and for identifying drug targets to drug leads, anti-infectives, molecular probes and insecticides.

Author contributions

VH: Writing – original draft, Writing – review & editing.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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