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The influence of ecological factors on cnidarian venoms

E.P. O'Hara *, D. Wilson, J.E. Seymour

Australian Institute for Tropical Health and Medicine, James Cook University, 1/14-88 McGregor Road, Smithfield, Qld, 4878, Australia

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ABSTRACT

Venom research is often focussed on medical relevance, novel compounds and venom evolution, whilst studying the relationship between a venom and its environment – venom ecology - has been conducted to a lesser extent. Given the projected environmental changes envisioned to occur with global warming, it is pertinent now more than ever, to highlight this topic. Here we review literature examining the influence of ecological factors such as environmental temperature, salinity, ontogeny, geographic location and diet on cnidarian venoms. This review provides an exclusive focus on the cnidarian phylum and encompasses all available published, peer-reviewed literature to our knowledge regarding the ecological factors influencing venom. We find a startling lack of research into the effects of both environmental and biological factors on venoms, with very few to no studies available per category. Importantly, research does exist that suggest these ecological processes may influence other marine or terrestrial venoms, thus we recommend future research is needed to explore this concept in cnidarians.

1. Introduction

Venomous species occur throughout many phyla in the animal kingdom, and some such as the Cnidaria (sea anemones, corals, jellyfish and hydrozoans) are solely composed of venomous animals (Goyffon, 2002). The defining characteristics of a venom have undergone much discussion within the literature and have been thoroughly reviewed with the following definition proposed: "a secretion, produced in a specialised gland in one organism, and delivered to a target organism through the infliction of a wound (regardless of how tiny it is); a venom must further contain molecules that disrupt normal physiological or biochemical processes so as to facilitate feeding or defence by the producing animal" (Fry et al., 2009). Venomous organisms are considered to be "active" when a toxin is produced in a gland or specialised tissue and then injected, whereas "passive" routes of exposure such as excretion are not truly venomous, although some overlap does occur (Goyffon, 2002).

The phylum Cnidaria boasts some of the most venomous animals in the marine environment, with the big box jellyfish *Chironex fleckeri* often revered as the most venomous animal on the planet (Endean, 1988). Unique to the cnidarians, specialised cells called cnidocytes contain stinging organelles called cnidae, characterised as either nematocysts, spirocysts, or ptychocysts (Hessinger and Lenhoff, 1988). The nematocysts are the only type that delivers venom.

The molecular composition forms part of the very definition of a venom (Fry et al., 2009), which highlights its importance as a research topic. How a venom effects its target – and incidentally humans – is determined by the molecules within the venom, and cnidarian venoms can have an array of effects. For example, the venom of the rhizostome jellyfish *Nemopilema nomurai* (initially misidentified as *Stomolophus meleagris*) has been shown to contain over 200 different toxins, with distinct functions such as potassium channel inhibitors, protease inhibitors, metalloproteases and hemolysins, among others (Li et al., 2014). Therefore, understanding the complexity that is venom composition is critical to understanding the venom as a functional whole. Whilst we understand the mechanisms of cnidarian venom delivery (Hessinger and Lenhoff, 1988; Nüchter et al., 2006; Schlesinger et al., 2009), there is a distinct lack of knowledge on how ecological factors – both biological and environmental – can influence the venom profile of these animals. For example, in *C. fleckeri* it has been shown that ontogeny and spatial distribution can affect variation in the venom, and it is further postulated that gender and/or environmental variations could be present (Winter et al., 2010). It could also be argued there is a distinct lack of knowledge of the comprehensive venom compositions. Some toxins have been identified, but the majority remain uncharacterised.

It is easy to assume an individual species will produce an individual venom, however here we present evidence that ecological factors can

* Corresponding author.
E-mail address: emily.ohara@my.jcu.edu.au (E.P. O'Hara).

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have a profound influence on intra-species venom variation. These variations will likely have ramifications for the ecology of the individual animal, the development of species-specific anti-venoms and searches for novel compounds. The importance of ecological influences on venom have been highlighted in two previous reviews. Geographic, ontogenetic and prey-associated venom variation within cnidarians has been highlighted (Ashwood et al., 2020), and venom evolution and gland morphology has been discussed in relation to ontogeny across terrestrial animals and cnidarians – with a primary focus on the sea anemone *Nematostella vectensis* (Surm and Moran, 2021). In this review we further expand and build upon these works to encompass more ecological factors, exclusively focusing on cnidarians but exploring a broader species diversity. The literature here is reviewed not from an evolutionary standpoint, but with a focus on plasticity within species venom composition and variation. Here the biological factors of diet and ontogeny, along with the environmental factors of salinity, environmental temperature and geographic location, are reviewed to determine their effects on cnidarian venoms. Appraisal of the knowledge gaps are highlighted, with specific note that some factors such as temperature and salinity are known to influence non-animal toxin production, but little to no research exists examining the influence of these environmental parameters on cnidarian venoms.

2. Biological factors

2.2. Diet

Research into the effect of diet on cnidarian venom is completely absent for early life stages and has only been described for two cubozoan species in the later life stages. However, venomous feeding structures in siphonophores have been described to change between species in relation to diet (Damian-Serrano et al., 2021).

Venom, cnidome and venom toxicity have been described to correlate to the feeding ecology of the big box jellyfish (*C. fleckeri)*, with toxicity changes corresponding to the increased need to capture vertebrate prey. In the study, dietary information from the literature was connected to the results observed for changes in the jellyfish's diet (McClounan and Seymour, 2012). Diet data has been collected from animals from multiple locations around Northern Australia (Darwin, Mission Beach and Townsville), which would indicate *C. fleckeri* as a species has a consistent diet at different locales within its distribution range (Carrette et al., 2002). However, no direct diet data, such as gut contents, was used to support conclusions on venom ontogeny (McClounan and Seymour, 2012).

Changes in venom composition of the jellyfish *C. barnesi* have also been linked to changes in the diet, with suggestion that compositional differences between immature and mature venom is due to the animal shifting from catching invertebrate to vertebrate prey (Underwood and Seymour, 2007). Again, no actual diet data is presented in support of this.

Diet specific venom has been evidenced and well-reviewed in numerous terrestrial animals, with implications that this could be a major driver in evolving venom composition (Casewell et al., 2013). It remains unclear why this field has been neglected in not only cnidarians, but the greater context of marine venoms. An obvious limitation of much of the available literature is the apparent reliance on literature sourced dietary data. With Lewis Ames and Macrander (2016) also emphasising that there are very limited accounts of cubozoan prey capture documented in natural settings. Whilst the studies presented here use the feeding ecology of the animals to rationalize results of venom differences, they are *not* inherently designing or analysing dietary experiments, i.e. not trialling different diets then analysing venom content, thus there is no control for confounding factors. It has previously been cautioned that captivity can influence venom quantity and quality, however, perhaps captive experiments may be the only way to control and test the effects of diet, as current in situ literature remains ambiguous (Kirchhoff et al., 2014; Modahl et al., 2010).

2.1. Ontogeny

There is a large amount of developmental diversity amongst cnidarians, which has been concisely summarised by Jouiaei et al. (2015). However, the available literature relating to venom ontogeny is dominated by sea anemones and jellyfish, of which the sexual reproduction involves the maturation of a gastrula to a planula in the development of cnidarians, which is then followed by two distinct stages: a sessile polyp and mobile medusa (both stages are not present in all cnidaria). When the available literature is combined, ontogenetic shifts in venom have been described spanning the entire cnidarian life cycle, albeit from a variety of species.

Venom analysis of the sea anemone *Nematostella vectensis* from gastrula to primary polyp found dramatic differences in toxin expression and nematocysts, between the gastrula, early planula, late planula, metamorphosing planula and primary polyp (Columbus-Shenkar et al., 2018). Behavioural predator-prey assays were also conducted to determine the ecological role of the observed changes in venom, evidencing that the venom of the planula repels larval fish upon ingestion, and can also paralyse *Artemia* nauplii. Molecular techniques were employed to visualise the expression of toxin genes throughout the life stages and have the potential to be applied to other venomous cnidarians (Columbus-Shenkar et al., 2018). Further to this work, additional toxin paralogs from *Nematostella vectensis* have more recently been shown to be present only in the early life stages, which themselves vary in toxicity to both fish larvae and arthropods (Sachkova et al., 2019).

Different types of nematocysts have been described in cnidarians and the presence and ratios of these different nematocysts have been shown to change during animal growth. Nematocysts are inherently linked to the production and injection of a cnidarian's venom, with differing types having been described to contain different venom (Carrette et al., 2002; Glasser et al., 2014; McClounan and Seymour, 2012; Wiebring et al., 2010), thus by analysing the occurrence of nematocyst types (the cnidome), changes in venom can be presumed. If we were to assume venom variation using nematocyst composition as proxy, the upside down jellyfish *Cassiopea xamachana* may display venom ontogeny. The proportions of nematocyst type vary within different life stages and the nematocyst bearing structures such as mucus and cassiosomes are life stage specific (Ames et al., 2020). The entire life cycle of the Irukandji jellyfish *C. barnesi* has been examined and shows new nematocyst types are added as the animal grows (Courtney et al., 2016). This variation in nematocyst presence is likely to result in variation in the venom composition of the animal's arsenal. The hatching planula contain one type (Courtney et al., 2016), primary polyps, immature medusa and mature medusa contain two types (Underwood and Seymour, 2007), and very large medusa contain three types (Pereira et al., 2010). These studies also highlight a common problem within nematocyst nomenclature. The two main types of nematocysts are called tumiteles and isorhizas (Courtney et al., 2016), or holotrichous microbasic rhopaloids and homotrichous haplonemes (Underwood and Seymour, 2007), and are actually identical nematocyst types classified differently by different authors.

Ontogenetic shifts in venom composition between immature and mature medusa of *C. barnesi* are evident (Underwood and Seymour, 2007), which is unusual as the nematocyst types present within the animal do not change as the venom changes (Underwood and Seymour, 2007). This challenges the common supposition that venom is nematocyst specific, indeed toxin variation within the same nematocyst type has been previously documented in a sea anemone (Columbus-Shenkar et al., 2018). Whilst nematocyst-specific venom has been documented in big box jellyfish (*C. fleckeri)* nematocysts (Carrette et al., 2002; McClounan and Seymour, 2012), it has previously been highlighted that scant data exist to support these assumptions in other species of cnidarians (McClounan and Seymour, 2012). Therefore, it remains possible

that, regardless of a stable cnidome in the early life stages (polyps and immature medusa) of *C. barnesi*, venom ontogeny may well still occur as seen in the later life stages. Further to this, very large mature medusa have been caught on occasion possessing an additional nematocyst type: the microbasic mastigophore (Pereira et al., 2010). There have been two confirmed deaths from an Irukandji sting (Fenner and Hadok, 2002) and skin scrapings from one of these victims (data not available for the second case) detailed nematocysts consistent with that found only in the larger medusa (Pereira et al., 2010). Whilst the venom from this new nematocyst has not been analysed, it is tempting to postulate it may contain more lethal toxins, hence the associated fatality. However, without comparable data from the only other mortality, the evidence to support this theory is anecdotal at best and would require further research to validate. Although, it would certainly be possible to screen large medusa specimens for this type of nematocyst and compare the venom.

Later life stages in the big box jellyfish (*C. fleckeri)* also present changes in venom with ontogeny. In direct comparison to the aforementioned *C. barnesi*, the switch in venom in this animal coincides with a change in cnidome at the 7–10 tentacles stage in the animal's life (McClounan and Seymour, 2012). This shift in venom was theorised to correlate with *C. fleckeri's* known feeding ecology, as the animal grows and begins targeting vertebrate rather than invertebrate prey (Carrette et al., 2002).

Whilst there is some documentation of cubozoan nematocysts in the very early life stages (Courtney et al., 2016), currently there is no literature examining the actual venom. Therefore, the stinging ability and/or potency of these early stages remains an unknown, presenting an opportunity for further investigation, especially concerning the more medically important species.

3. Environmental factors

Whilst biological influences on venom have been covered to some extent within the literature, research into the influence of environmental factors such as geography, salinity and temperature is sorely lacking. What is currently known on the influence of environmental factors is reviewed here.

3.1. Geographic location

Venom variation in cnidarian specimens over small-scale geographic distances has been explored, whereby the venom of the cubozoan *C. fleckeri* was found not to vary between regional geographic locations (less than 70 km distance) (McClounan and Seymour, 2012). Marine venoms from other sources, such as the cone snail *Conus vexillum*, do vary between geographic locations of comparable distances (Abdel--Rahman et al., 2011). Whilst no variation was seen over small distances, the composition of *C. fleckeri* venom does differ between larger national geographic locations with differences observed in animals from an estimated range of over 500 km across Northern Australia (Winter et al., 2010).

Similar geographic distances have been explored in regard to the venom composition and toxicity of the giant jellyfish *Nemopilema nomurai,* which has been analysed for animals caught at multiple locations throughout the Yellow Sea (Yue et al., 2019). No effects of geographic location could be established, however dramatic venom variation was found between individuals. Whilst the authors describe compositional and toxicity differences between the venom of two animals caught at the same location, the cause of these variances remained inconclusive. The sampled locations spanned approximately 800 km, but the giant jellyfish has been described to be widely distributed in the Yellow Sea due to currents and the swimming ability of the animals (Yue et al., 2019). These results may potentially reflect an overlap in the ranges of these animals, and the described differences between animals from the same location could be attributed to such an overlap spanning sample locations.

Additionally, toxin gene expression within the sea anemone *Nematostella vectensis* has been examined between animal populations >900 km (estimated) apart. This is the only evidence of a controlled environment study, whereby the separate populations were raised in identical conditions, in which toxin gene expression from each population was measured in response to heat shock and salinity. It has been described that *N. vectensis* animals from North Carolina express toxin genes differently in response to heat stress than those from Massachusetts (Sachkova et al., 2020). Whilst not a comparison of standard venom content across location, the authors describe that populations from different climatic conditions respond differently to heat stress (Sachkova et al., 2020), thus evidencing the ecological significance of cnidarian venom plasticity.

Lastly, geographical venom differentiation has been identified at very large-scale distances in one species of sea anemone, *Bunodosoma caissarum* (Orts et al., 2013). Two "geographically distant" populations were analysed, from the south coast of Brazil and an archipelago separated by over 3000 km. Reversed-phase high performance liquid chromatography (rp-HPLC) analysis showed similar venom profiles between both locations, however, only two toxins have currently been characterised for this species, one of which was absent from the archipelago venom profile, evidencing there are distinct differences in the venom between these locations. This work specifically notes that ecological and genetic factors could not be controlled, but venom collection and animal size was standardised. Previous work with *C. fleckeri* (Winter et al., 2010) discusses the possible impacts of having analysed jellyfish of different sizes (due to size varying with location), but as evidenced here with *B. caissarum* (Orts et al., 2013) it could be that even if size was standardised, location related differences in the venom would still have been found. Whilst *C. fleckeri* are known to change venom with age (McClounan and Seymour, 2012) the fact that their size is location related suggests they are still reaching peak maturity, they are just smaller.

Little to no literature exists pertaining to hydrozoans, with only an incidental mention in otherwise focussed research in which hydrocorals have been described to maintain similar toxic effects regardless of location (García-Arredondo et al., 2015). However, this appears to be in reference to multiple papers (Middlebrook et al., 1971; Wittle et al, 1971, 1974) that describe the general mode of toxic effects of *Millepora* species, with each study sampling at a different location and/or contrasting different species, rather than comparing the venom of a single species across location.

Geographic venom variation in true anthozoan corals – rather than the hydrocorals – has been studied to a slightly greater extent, though research is still lacking. Indeed true venom analysis is rarer still, with most available literature examining whole body extracts in lieu of specific venom extraction. The global proteome (the total complement of proteins in the venom) from the heterotrophic coral *Tubastraea coccinea* has been shown to change over time, if a population is transplanted from one geographic location to another (separated on a small regional scale ~40 km). However, the actual composition of toxic venom components remained identical in all populations, thus evidencing no change (Kitahara et al., 2020), which is interesting as the authors specifically note very different environmental conditions between the two sites. This lack of venom change is consistent with the findings of McClounan and Seymour (2012) in the analysis of the previously mentioned *C. fleckeri* venom over small geographic scales. This however cannot be interpreted as a cnidarian specific pattern across small distances, as local (Harvell et al., 1993) and even intracolonial (Gunthorpe and Cameron, 1990) toxin variation has been described in other corals. In the West Indian gorgonian coral *Briareum asbestinum* the overall defensive chemistry – rather than venom only extract – differs not only substantially between Bahamian colonies and US Virgin islands colonies, but also between individual Bahamian colonies (Harvell et al., 1993). A range of scleractinian corals (*Lobophyllia corymbosa, Favites abdita, Favia matthaïi,*

Favia stelligera, Platygyra daedalea, Leptoria phrygia, Cyphastrea serailia, Hydnophora exesa and *Astreopora myriophthalma*) further demonstrate intracolonial toxin variation over time, with successive extracts of each colony displaying different toxic activity profiles (Gunthorpe and Cameron, 1990). The latter of which should actually serve as a cautionary note when interpreting the plasticity of toxic activity in cnidarians, given this temporal propensity to change after sampling.

Geographic locations are inferred very differently within the literature, with analysis conducted on a broad diversity of scales which needs to be considered when interpreting the presence/absence of venom variation. At greater distances it may logically be expected to see differences, as populations are more separate. However, none of the research presented here actually controls for influencing factors to just analyse geography, e.g. collecting animals from separate locations, raising them in identical conditions to determine if the geographic location is solely responsible rather than the changing environment that comes with changing location. Only one study acknowledged that ecological and genetic factors could not be standardised (Orts et al., 2013), although similar research with cone snails (Duda and Lee, 2009) did analyse the mitochondrial locus of animals to determine that genetic differentiation was not responsible for the observed venom differences, suggesting that the environmental conditions may be responsible rather than genetic drift between separate locations. Geographical distance, especially at the smaller regional scale, appears not to be a reliable indicator for predicting geographical venom differentiation. Whilst the literature showed venom differences between all largely separate areas (thousands of km), cnidarian venom does not seem to be influenced on a smaller scale. However, this conclusion should be interpreted cautiously, given the small amount of research available.

3.2. Salinity

All marine organisms are exposed to the differences salinity induces on ecosystems, but literature regarding the effect on venom/toxins is only available for the non-animal toxins. Whilst the primary focus of this review is on actively venomous cnidarians, some inclusion of other passive forms (e.g. toxic dinoflagellates) was deemed necessary where literature was completely absent for true venoms, but existed for passive toxins. Cnidarians have an intrinsic link with algal and dinoflagellate species, as numerous cnidarians host these as symbionts. Whilst these symbionts are located in the very tissue of cnidarians, they are still exposed and respond to varying changes in salinity, as evidenced by salinity induced bleaching (Kerswell and Jones, 2003). Whilst this is no means an ideal proxy, we do know algae and dinoflagellates within cnidarian tissue can be physically influenced by salinity, therefore the toxins contained within these same invertebrate tissues, and indeed the invertebrates themselves (which ultimately control the production of toxins), have the same potential to react to salinity. As such, non-animal non-cnidarian toxins are briefly discussed here.

Salinity affects toxins in various ways, sometimes specific to species, sometimes to individual strains, with no one prevailing trend. Multiple studies found that salinity affects the toxins of the dinoflagellate *Alexandrium minitum,* with toxicity and toxin content increasing with salinity (Grzebyk et al., 2003; Hwang and Lu, 2000; Lim and Ogata, 2005), yet a later study contrastingly reported no effect of salinity in the same species (Lim et al., 2011). Similarly, within the cyanobacterium *Nodularia spumigena,* whilst literature determines that salinity does effect toxins, each available study describes a different effect (Blackburn et al., 1996; Hobson and Fallowfield, 2003; Mazur-Marzec et al., 2005). Whilst the multitudes of contrasting results may initially seem unhelpful, they actually serve to highlight the point that salinity is affecting these toxin-producing organisms in very diverse ways, suggesting that the ecology of the organism is being influenced right down to a strain specific level.

The salinity/toxin relationship can also provide further insights into the ecology of an organism. The toxin content of *A. minitum* was much higher in offshore seawater and was all but zero in estuarine seawater, however, as *A. minitum* grew well in both salinities, the authors hypothesized that "toxin biosynthesis was greatly weakened due to the lack of amino acid precursors in prey material" (Grzebyk et al., 2003). This theory could also be applicable to animal venoms.

It has been suggested that research in this field is inherently flawed as cell size would naturally vary with physical environmental changes and thus toxin content would change with cell size (Granéli and Flynn, 2006), an argument also relevant to animal venoms/toxins. However, multiple studies have considered this and present results that contradict the criticism, evidencing that cellular toxin quota was not affected by salinity-dependent growth rate, nor did toxin profiles change with salinity (Lim et al., 2011). Indeed, the toxin content of some species can peak at sub-optimal growth salinity (Lim and Ogata, 2005). Additionally, in the dinoflagellate *A. fundyense*, there is no relationship between photosynthesis or growth with toxicity, and the authors ultimately hypothesized that toxicity is at least partly driven directly by environmental conditions (Etheridge and Roesler, 2005). This hypothesis should be emphasized across all toxicity studies and should be used to explore the knowledge gap concerning other toxin and/or venom wielding marine organisms.

Research into the effect of salinity on the venom/toxins of not only cnidarians, but marine animals as a whole is scarce. Only one study could be found examining this in zootoxins, in which toxin gene expression was analysed in the sea anemone *Nematostella vectensis* (Sachkova et al., 2020). Although this was analysed in relation to population specific adaptations to salinity stress, rather than a salinity oriented study, it demonstrated that reduced salinity stress causes varying levels of toxin gene expression in a number of geographically separated sea anemone populations, suggesting salinity is a contributing ecological factor in venom/toxin production.

The evidence of salinity as an influencing factor to algal toxicity is vast, so why this has not been explored further within animal toxins/venom is perplexing. Indeed, multiple studies control for salinity when analysing venom (Dutertre et al., 2010; Hoepner et al., 2019; Sivan et al., 2010), presumably to mitigate its influence, yet there is very little research into its effect.

3.3. Temperature

Variation in toxin/venoms with environmental temperature is all but unheard of within zootoxins, although some research has been conducted with snake venoms (Yin et al., 2020), but has been better documented within non-animal toxins (Band-Schmidt et al., 2014; Gedaria et al., 2007; Lim et al., 2006), posing a compelling argument that similar effects could be seen in animal venoms and warrants further investigation.

Only two studies could be found that analyse the influence of environmental temperature on cnidarian toxins. Firstly, toxins in the sea anemone *Actinia equina* have been analysed using Reverse Transcription quantitative Polymerase Chain reaction (RT-qPCR), to quantify the expression of toxin genes over different temperatures (O'Hara et al., 2018). The study aimed to assess long-term temperature change to reflect projected temperature changes with global warming. The anemones were held for 5 months at experimental temperatures to negate the possibility of results relating to thermal shock response. The expression of two toxin genes, equinatoxin and equistatin, were observed to change at 10 °C and 22 °C compared to a 16 °C control, although only the colder temperature was reported as significant downregulation in both genes. Whilst not statistically significant, it is interesting to note the two toxin genes displayed opposite trends in relation to the warm treatment, suggesting the ecological response of the anemones to environmental temperature change is toxin specific (O'Hara et al., 2018). This evidenced for the first time that environmental temperature does influence toxin production in cnidarians. *A. equina* is a common and relatively harmless cnidarian, but provides a

foundation to continue work with species that pose a threat to human health.

Secondly, toxin gene expression in the sea anemone *N. vectensis* was analysed in response to short-term (24hr) environmental heat stress (Sachkova et al., 2020). As also noted in the geographic location and salinity sections of this review, it has been described that sea anemone populations from different climatic conditions respond differently to heat stress in relation to venom production. Strong evidence highlights that the thermal ecology of the animal plays a role in toxin gene expression, as the thermal regimes differ between *N. vectensis* habitats, and those populations not naturally exposed to higher temperatures respond differently in their toxin gene expression (Sachkova et al., 2020).

We can therefore conclude that environmental temperature can impact cnidarian venom toxins in both short term (Sachkova et al., 2020) and long term (O'Hara et al., 2018) instances. Whilst the gene analysis of the two studies was quantitative, changes in the venom toxicity were not analysed, so it remains unknown what precise ecological impacts the changes in the toxins have. However, the study on *N. vectensis* (Sachkova et al., 2020) did include at least some proteomic analysis by LC-MS/MS that showed very similar trends to the transcriptomic analyses.

Overall, we highlight the knowledge gap for venom/toxin work in relation to environmental temperature, most especially in medically socio-economically important cnidarian species, given evidence from less potent species suggests temperature does affect venom composition.

4. Conclusion

Whilst the literature is scattered across taxa, often with each species only receiving sparse dedicated analysis, it is evident that ecological parameters do affect cnidarian venom composition, albeit in very different and often unpredicted ways. The challenge now is to use this knowledge to advance the field of venom research and tease out the effects these parameters may have on venom profiles.

There is large amount of evidence detailing that environmental temperature and salinity can influence toxins in non-animal organisms such as dinoflagellates, whereas no comparable research exists for zootoxins. Given sea surface temperature and salinity are parameters predicted to change with global warming forecasts, it would seem these are the urgent areas required to be explored in the animal venoms if we are to stand a chance at predicting changing venom ecology. It is interesting that environmental temperature has not previously been analysed along with venom, as venomous animals have been noted to predominantly reside in intertropical areas of the world (Goyffon, 2002) suggesting an innate or even evolutionary relationship between venom and temperature.

The value of ecology is largely overlooked in medical research, however as evidenced here it has the ability to drastically influence the venom of some of the most dangerous cnidarians on the planet. One clear example is the urging conclusion within a medical research journal for the need to conduct venom studies on Irukandji jellyfish in order to develop preventive strategies and effective treatments (Fenner and Hadok, 2002). Venom studies alone will not be sufficient. The ecology and toxicology must unite, the understanding of how venom changes with ecology must come first, as medical treatments cannot advance if we do not acknowledge the two are inherently linked. The two fields need to coalesce, as working separately has led to drastic gaps in our understanding, leaving us unprepared to predict how a changing environment will affect the severity of human envenomations by dangerous cnidarians.

Through the compilation of literature presented here, we see there is a very real link between a cnidarian's venom and its ecology. The plasticity of these venoms across both biological and environmental factors is astounding, especially given the very simple nature of the organism themselves. This is a concept that will affect not only our understanding of medical treatments, but also our knowledge of the fundamental ecology of the animals themselves. A rather daunting prospect is that if venoms can indeed change with changing environments, we may well begin to see heretofore relatively harmless cnidarians begin to exhibit more hazardous traits as the world changes around them.

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