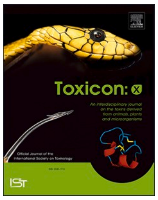
Toxicon:X 13 (2022) 100094

Contents lists available at ScienceDirect

Toxicon: X

journal homepage: www.journals.elsevier.com/toxicon-x



Review

Implications of bleaching on cnidarian venom ecology

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ARTICLE INFO

Handling Editor: Dr. Ray Norton

Keywords:
Stress
Energy budget
Symbiosis
Nematocyst
Physiology

ABSTRACT

Cnidarian bleaching research often focuses on the effects on a cnidarian's physiological health and fitness, whilst little focus has been towards the impacts of these events on their venom ecology. Given the importance of a cnidarian's venom to their survival and the increasing threat of bleaching events, it is important to understand the effects that this threat may have on this important aspect of their ecology as it may have unforeseen impacts on their ability to catch prey and defend themselves. This review aims to explore evidence that suggests that bleaching may impact on each of the key aspects of a cnidarians' venom ecology: cnidae, venom composition, and venom toxicity. Additionally, the resulting energy deficit, compensatory heterotrophic feeding, and increased defensive measures have been highlighted as possible ecological factors driving these changes. Suggestions are also made to guide the success of research in this field into the future, specifically in regards to selecting a study organism, the importance of accurate symbiont and cnidae identification, use of appropriate bleaching methods, determination of bleaching, and animal handling. Ultimately, this review highlights a significant and important gap in our knowledge into how cnidarians are, and will, continue to be impacted by bleaching stress.

1. Introduction

Cnidarians are collectively a diverse group of highly successful, ancient, aquatic organisms. Molecular evidence suggests that the earliest cnidarians appeared some 740 million years ago (Park et al., 2012), making them the oldest lineage of venomous animals on Earth. In the 200 million years that followed, the phylum underwent significant diversification (Park et al., 2012), and today consists of 14,866 accepted species (WoRMS, 2021), taxonomically divided across three clades; Anthozoa (corals and sea anemones), Medusozoa (jellyfish and hydras) and Endocnidozoa (parasites) (Fig. 1). Together, cnidarians' have a global distribution and may be found occupying a diverse range of marine and freshwater environments including shallow coral reefs, deep polar seas or freshwater lakes and streams.

A defining feature shared amongst all cnidarians are the presence of cnidocytes. Cnidocytes are specialized cells located predominately within the epidermal tissue (Fautin, 2009) (Fig. 2), that contain complex, subcellular organelles called cnidocysts (or cnidae). Cnidae, are typically described as tiny (3–250 μm), collagenous capsules, comprised of a tightly coiled thread (Mariscal, 1974; Weill, 1929) (Fig. 2d). Activation of the cnidae by physical, chemical, and neurological stimulation (Kass-Simon and Scappaticci, 2002), triggers a dramatic release of the internal pressure, leading to the explosive discharge of the thread from within the capsule (Nüchter et al., 2006; Weber, 1989) (Fig. 2e).

Cnidae are generally described as either penetrative and liquid toxin-filled, ensnaring and/or sticky. Differences in the ecological and functional roles of the cnidae are thought to contribute to the significant diversity in morphology seen between them (Kass-Simon and Scappaticci, 2002). There are some 28 types of cnidae, which have been classified as either spirocysts, ptychocysts or nematocysts, based on the characteristics of secondary structures contained within the cnidae (Cutress, 1955; England, 1991; Mariscal, 1974; Rifkin, 1996; Weill, 1929).

Nematocysts are of particular importance to the success of cnidarians. Many nematocysts (eg. euryteles, stenoteles and mastigophores) are highly sophisticated toxin-filled, micro-weapons, equipped with purpose-built barbs and spines. The force at which the thread is expelled allows these nematocysts to penetrate and bore into tissue, and act as a direct pathway for the toxins to be released, which in turn subdues and/or kills the organism (Ewer, 1947; Hessinger and Lenhoff, 1973; Honma et al., 2005; Mariscal, 1974; Tardent, 1995).

The toxins (or venom) that are injected by the nematocysts, are a

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https://doi.org/10.1016/j.toxcx.2022.100094
Received 15 November 2021; Received in revised form 14 January 2022; Accepted 23 January 2022

complex cocktail of bioactive proteinaceous (peptides, proteins, enzymes), small molecules, non-proteinaceous substances, salt, and water (for examples, see reviews: D'Ambra and Lauritano, 2020; Frazão et al., 2012; Fu et al., 2021; Jouiaei et al., 2015b; Picken and Skaer, 1966). The toxicity and potency of a cnidarian venom is the result of the unique composition toxins and the intended effect on the prey and/or predators when injected (Klompen et al., 2018). It is well documented that cnidarian venoms often exhibit cytotoxic, neurotoxic and cardiotoxic bioactivities (D'Ambra and Lauritano, 2020; Jouiaei et al., 2015b; Mariottini and Pane, 2014), and as such are capable of inducing pain, paralysis, and/or tissue lysis in affected organisms (Ashwood et al., 2020; Jouiaei et al., 2015b). Together, the nematocysts and accompanying venom are an integral part of cnidarian venom ecology: the way in which they are able to defend against, prey upon, and spatially compete with other organisms within their environment (Jackson et al., 2019).

The nematocyst-derived venom of some species are also complimented by toxins that are secreted from ectodermal gland cells (Moran et al., 2012;Zhang et al., 2003). Although these toxins have been shown to be absorbed by potential prey, whereby inducing neurotoxic effects (Moran et al., 2012), and as such, may have an important ecological role, these toxins are not associated with any specific mechanism of delivery (eg. fangs, stingers, teeth etc.), and therefore lack the ability to be injected directly through an inflicted a wound. To this end, such toxins are currently not believed to meet the accepted criteria used to define toxins as a 'venom' (Casewell et al., 2013; Fry et al., 2009), and may better described as a 'poison'. These toxins will therefore not be discussed in this review hereafter. Though, the potential for such toxins to also be impacted by stressors such as bleaching should not be ruled out.

In addition to the cnidarian's unique venom delivery system, the success of many cnidarian's may also be largely attributed to the mutualistic relationship they have with a photosynthetic unicellular golden-brown dinoflagellates, *Symbiodinium* spp. (zooxanthellae) (Fournier, 2013; Lesser et al., 2013) (Fig. 2b). While this relationship is most famously known to occur within hermatypic (reef-building) corals (Scleractinaria), this symbiosis has also been documented in ahermatypic anthozoans (Actiniaria, Corallimorpharia and Octocorallia) and Medusozoans (Scyphozoa, Hydrozoa and Cubozoa) (Djeghri et al., 2019; Jahajeeah et al., 2020; Muscatine, 1974). Indeed, this cnidarian-*Symbiodinium* symbiosis is reported in 13 of 23 cnidarian orders (Muscatine, 1974), with close to 50% of all cnidarians' exhibiting this photo-symbiosis (Douglas et al., 1993; Sikorskaya and Imbs, 2020) (Figs. 1 and 2a).

Symbiodinium spp. are housed within special vacuole compartments, called symbiosomes, within the host cnidarian cells, localised to the gastrodermis tissue (Mansfield and Gilmore, 2019; Trench, 1979; Yellowlees et al., 2008) (Fig. 2c). Under optimal conditions, the *Symbiodinium* spp. may occur in densities exceeding 1–2 million cells. cm^{-2} of tissue surface (Drew, 1972; Van Oppen and Medina, 2020; Wooldridge, 2013), equating to an average of 1–2 symbionts per host cell (Muscatine et al., 1998).

This relationship is mutually beneficial to both participants. While the *Symbiodinium* spp. receive inorganic nutrients and safe refuge from herbivory (Weis, 2008), the cnidarian hosts are provided with photosynthetic by-products (sugars, amino acids, carbohydrates and small peptides (Muscatine, 1967, 1990), which contribute up to 95% of all their daily metabolic energy needs (Falkowski et al., 1984; Muscatine et al., 1981; Muscatine and Porter, 1977).

The cnidarian-*Symbiodinium* relationship is fragile, and fluctuations to environmental and abiotic factors such as temperature, solar irradiance, salinity, nutrients, sedimentation and chemical pollutants may throw the relationship out of balance, alter metabolic and cellular processes and ultimately lead to oxidative stress in both the cnidarian and symbiont (Baird et al., 2009; Cziesielski et al., 2019; Douglas, 2003; Fournier, 2013; Lesser, 2011; Morrow et al., 2018; Suggett and Smith, 2020). In an attempt to protect themselves from further oxidative stress, cnidarians will expel the *Symbiodinium* spp. from their tissue (Weis, 2008). In the absence of their symbionts, the cnidarians become distinguishably clear, opaque or white. It is due to this confronting loss of colour and pigment that this phenomenon has been called 'bleaching'

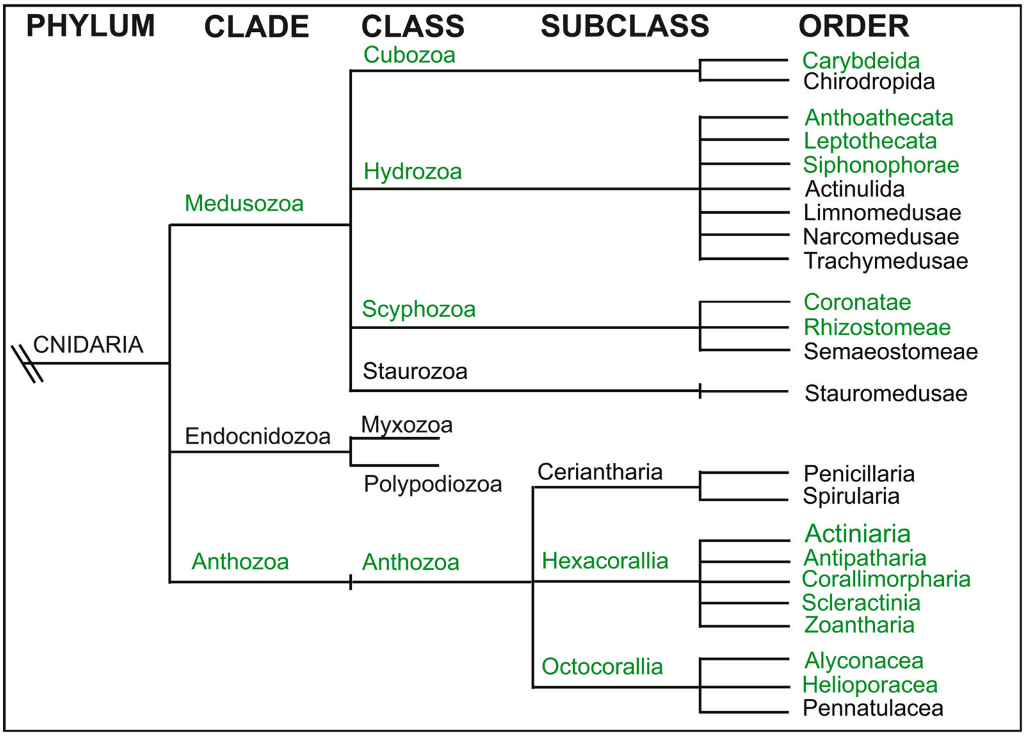

Fig. 1. Phylogeny of phylum Cnidaria (WoRMS, 2021). Taxa identified to have a symbiotic relationship with *Symbiodinium* sp. are highlight in green (Djeghri et al., 2019; Jahajeeah et al., 2020; Muscatine, 1974).

(Douglas, 2003). It is largely accepted that all symbiotic cnidarians are susceptible to bleaching, as such, bleaching has been demonstrated in scleractinian, octocorallian, actiniarian, corallimorpharian, zoanthid, hydrozoan and scyphozoan species (Djeghri et al., 2019; McClanahan et al., 2018).

In addition to the loss of colour, the loss of the photo-symbionts means that bleached cnidarians consequently also lose a significant proportion of their energy input that the symbionts provide (Gundlach and Watson, 2019; Morris et al., 2019). This energy deficit leads to a range of sub-lethal effects including; significant reductions in tissue thickness (Ainsworth et al., 2008; Baird and Marshall, 2002; Szmant and Gassman, 1990), size (Klein et al., 2019; McGill and Pomory, 2008), growth (Carilli et al., 2009; Goreau and Macfarlane, 1990), reproduction (Baird and Marshall, 2002; Mendes and Woodley, 2002; Michalek-Wagner and Willis, 2001a, 2001b; Szmant and Gassman, 1990) and recruitment (Gilmour et al., 2013; Mallela and Crabbe, 2009). If unfavorable environmental conditions persist, and if the cnidarians are unable to reacquire the photo-symbionts and recover, the cnidarians' fitness will continue to decrease, and they become increasingly susceptible to disease (Miller et al., 2009) and mortality (McClanahan et al., 2004; Tkachenko et al., 2007).

As the world's oceans continue to be threatened by climate change and cumulative anthropogenic stressors, cnidarians are becoming increasingly susceptible to bleaching (Oliver et al., 2018). Worryingly, we know very little as to how such bleaching might impact on the venom ecology of photo-symbiotic cnidarians. This review aims to explore the evidence, albeit limited, and synthesize the current understanding on how a cnidarians' venom ecology may be impacted by bleaching stress. Possible mechanisms and nuances that may be driving these changes are also explored and considerations for future works in this area are also provided. A brief summary of critical background knowledge, fundamental to the understanding of cnidarian venom ecology, is also given.

2. Cnidarian venom ecology

The subject of cnidarian venom ecology is complex. Consideration must be made to not only the venom, but also to the corresponding cnidae present. Furthermore, significant variations occur in both the cnidae and venom between species, but also intra-specifically and indeed within a single individual. In addition, both cnidae and venom have been shown to vary temporally, exhibiting plastic responses, sometimes independent to one another, to a range of biological and environmental factors.

2.1. Cnidae

There is considerable variability in the presence of each nematocyst type between and within taxa. Different species, even those closely related, exhibit differences in the characteristics of their nematocysts and cnidoms (Östman, 2000). These differences have been recognized as a valuable tool in the taxonomic identification of species (Carlgren, 1949; den Hartog, 1980; Gershwin, 2006; Östman, 2000; Stephenson, 1929; Weill, 1929; Williams, 2000). Many cnidarians are observed to possess multiple types of cnidae, often with specific cnidae localised to distinct anatomical regions within the body (Ashwood et al., 2020; den Hartog, 1980; McClounan and Seymour, 2012; Prentis et al., 2018; Shick, 1991; Strömberg and Östman, 2017). The specificity of cnidae within regions of the body are presumed to be due to their intended function and purpose (Shick, 1991). Furthermore, a species cnidom – the specific completement of cnidae present within a species – may change throughout various stages of the organism's life history (Weill, 1929), and a single species may also have different size classes of the same type of nematocysts (Acuña et al., 2007; den Hartog, 1980; Mariscal, 1974).

2.2. Venom

Similarly to cnidae, there is significant variation in venom profiles between cnidarian taxa (Ashwood et al., 2020), but also intra-specifically both between and within geographic locations (Mitchell et al., 2020; Winter et al., 2010; Yue et al., 2019). Furthermore, venom variation has also been shown to occur within different anatomical structures within individuals (Klompen et al., 2018; Little et al., 2020; Macrander et al., 2016; Mies et al., 2017; Mitchell et al., 2017). This variation is believed to reflect the changes in the cnidom that arise due to specific ecological functions of different areas of the body (Ashwood et al., 2020; Little et al., 2020; Prentis et al., 2018;

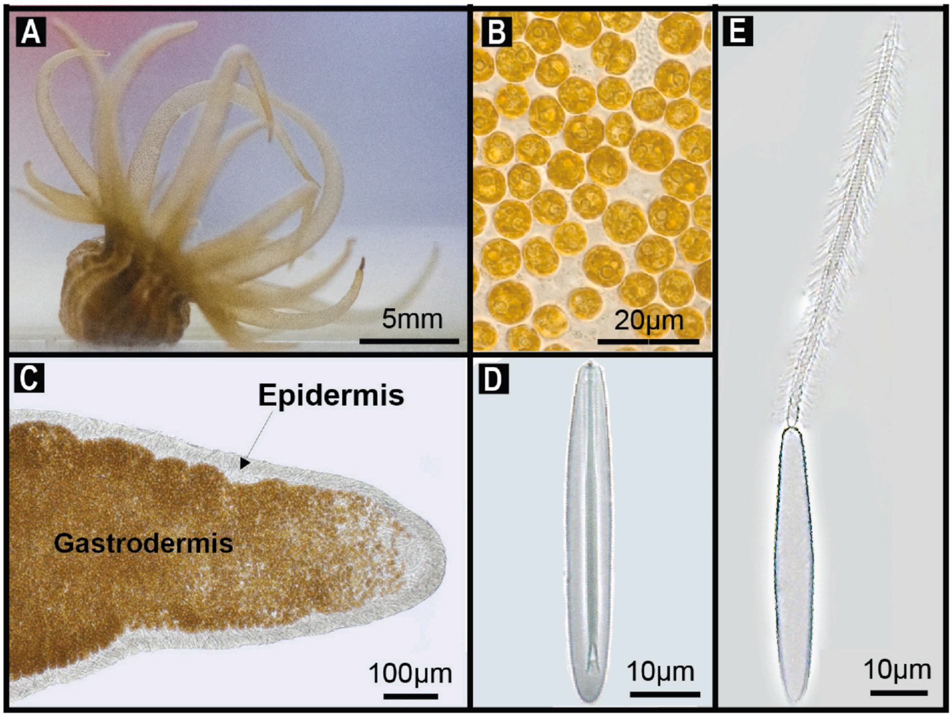

Fig. 2. Cnidarian symbiosis and cnidae. A. *Symbiodinium* sp. can be seen as the brown pigments within the tissue of a photosymbiotic *Aiptasia* sp.; B. *Symbiodinium* sp. from within tentacles of *Aiptasia* sp. (x63); C. *Aiptasia* sp. tentacle whereby *Symbiodinium* sp. are shown to reside within the gastrodermis, whilst cnidae are extensive throughout the epidermis (x10); D. undischarged nematocyst from *Aiptasia* sp. acontia filament (x63); E. discharged nematocyst (equipped with dense spines along the expelled shaft) from *Aiptasia* sp. actonia filament (x40). Photo credits: Katrina L. Kaposi.

Schendel et al., 2019). It has also been found that the composition of the venom within an individual may also vary between different nematocysts types (McClounan and Seymour, 2012). Furthermore, cnidarian venoms have been shown to exhibit ontogenetic change, independent to, and in the absence of, any changes to the cnidae and cnidoms themselves (Underwood and Seymour, 2007). It is therefore evident that each cnidae and venom type have a specific function and role and that changes to either of these may have significant implications on the survival of such species within their environment.

2.3. Plasticity

A range of ecological factors have been shown to impact on the venom profile and expenditure in cnidarians (O'Hara et al., 2021). Briefly, venom variations and/or changes have been attributed to differences in temperature (Jouiaei et al., 2015a; O'Hara et al., 2018; Oakley et al., 2017; Richier et al., 2008; Sachkova et al., 2020; Sunagawa et al., 2009), age (Columbus-Shenkar et al., 2018; Klompen et al., 2018; McClounan and Seymour, 2012; Underwood and Seymour, 2007), diet (Underwood and Seymour, 2007), location (Winter et al., 2010; Yue et al., 2019), salinity (Sachkova et al., 2020), ultraviolet radiation (Richier et al., 2008; Sachkova et al., 2020), interspecies competition (Yosef et al., 2020) and predation pressure (Ben-Ari et al., 2018).

Similarly to venom, cnidom plasticity has also been documented in response to a number of biotic factors such as age and size (Carrette et al., 2002; Higgins et al., 2008; Kramer and Francis, 2004; McClounan and Seymour, 2012; O'Hara, 2018; Paruntu et al., 2000; Zenkert et al., 2011). Cnidom ontogeny, the change in the types and/or distribution of cnidae with age, has been reported in both medusozoans (Carrette et al., 2002; Higgins et al., 2008; McClounan and Seymour, 2012), and anthozoans (Paruntu et al., 2000; Zenkert et al., 2011). Similarly, the size of the polyp, at least in some species, may also influence the size of the nematocysts present (Chintiroglou et al., 1997; Kramer and Francis, 2004).

The conditions in which cnidarians are subjected to may also influence their cnidom (Cerrano et al., 1997; Gochfeld, 2004; Jennings, 2014; O'Hara, 2018). There is evidence to show that both temperature (O'Hara, 2018) and water movement (Cerrano et al., 1997) may impact on the cnidoms of actinarians and hydrozoans respectively. Furthermore, when cnidarians perceive themselves to be under increased threat of predation, either natural or artificial, their cnidom may change significantly (Gochfeld, 2004; Jennings, 2014). Corallivory grazing by butterflyfish (*Chaetodon multicinctus*) saw a significant increase in microbasic p-mastigophores by *Porites compressa* (Scleractinaria) (Gochfeld, 2004). Conversely, whilst predation on *Aiptasia pallida* (syn. *Exaiptasia diaphana*) (Actiniaria) resulted in significantly less nematocysts overall, artificial damage induced an increase in microbasic p-mastigophores (Jennings, 2014).

Together, the evidence provided here demonstrates how dynamic and complex cnidarian venom ecology is. As variations in cnidae and venom have been shown to occur both spatially and temporally and in response to changes within the environment, it is not without reason to hypothesise that significant stressors, such as bleaching, may also impact on the venom ecology of cnidarians.

3. Effects of bleaching on cnidarian venom ecology

Of manipulative cnidarian bleaching stress experiments that seek to understand the impacts of bleaching on the physiology, health and fitness of cnidarians, the dependent response variables often measured typically include mortality, skeletal growth, respiration, energy reserves, rate of heterotrophy, growth and/or reproduction (McLachlan et al., 2020). Despite the ecological importance of a fully functional venom delivery system, it is surprising how few studies have attempted to look at how bleaching may impact on the cnidae and/or venom of bleached photo-symbiotic cnidarians. Indeed, only six research papers within the literature have been found to meet the criteria of comparing the effects on bleaching on either the cnidom, venom profile or toxicity, either over time (Hoepner et al., 2019), or as direct comparisons to an unbleached cohort (García-Arredondo et al., 2011; Gundlach, 2018; Gundlach and Watson, 2019; Hernández-Elizárraga et al., 2019; Olguín-López et al., 2019).

3.1. Effects on cnidom

Bleaching has the potential to impact on the cnidae of photo-symbiotic cnidarians. To date, this has been demonstrated with significant changes shown to occur within the cnidoms of two sea anemone species (*Entacmaea quadricolor* and *Exaiptasia diaphana*) (Gundlach, 2018; Gundlach and Watson, 2019; Hoepner et al., 2019). In the case of *E. quadricolor,* prolonged (five month) bleaching was shown to cause the overall density of cnidae to increase, peaking at 8 and 14 weeks before reducing slightly, yet remaining greater than initial densities (Hoepner et al., 2019). Conversely, when the density of cnidae for *E. diaphana* was assessed, it was found that bleaching did have an effect (Gundlach and Watson, 2019). However, bleaching also resulted in a significant increase in the number of spirocysts and a subsequent decrease in the number of penetrative nematocysts (identified as microbasic p-mastigophores and basitrichous isorhizas) (Gundlach and Watson, 2019). The size and quality of these penetrative nematocysts, particularly microbasic p-mastigophores, in bleached specimens were compromised, inferred by smaller size (volume) and increased abnormalities (deformed capsules and tubules), than unbleached counterparts (Gundlach, 2018; Gundlach and Watson, 2019). These abnormalities were believed to render the nematocysts ineffective, and consequently a reduction in the ability to catch live prey was observed (Gundlach, 2018). It is therefore clear from these studies that bleaching is able to impact on the density, ratio, size, and quality of cnidae. In turn, such changes have the potential to directly impact on a cnidarians' ability to feed and defend itself.

3.2. Effects on venom composition

Bleaching has been shown to not only impact on the cnidarian venom apparatus system, but to also compromise the ability of cnidarians to produce venom (Hoepner et al., 2019), and also change the properties within the venom itself (García-Arredondo et al., 2011; Hernández-Elizárraga et al., 2019; Hoepner et al., 2019). Bleaching resulted in the volume of lyophilized crude venom of *E. quadricolor* (Actiniaria), which was collected monthly over a period of five months, to reduce significantly with time (Hoepner et al., 2019).

Bleaching has also been shown to have mixed effects on the overall protein concentration of cnidarian venom (García-Arredondo et al., 2011; Hernández-Elizárraga et al., 2019; Hoepner et al., 2019; Olguín-López et al., 2019). Despite significant reductions in volume of crude venom that was collected from bleached sea anemones, the venom that was obtained nine weeks after the onset of the prolonged bleaching study, was shown to have a higher concentration of protein (Hoepner et al., 2019). The elevated protein concentrations began to normalize in the weeks and months that followed and were comparable to initial concentrations by week 13 (Hoepner et al., 2019). Contrary to these results were the findings that in two hydrozoan species (*Millipora complanata* and *Millipora alcicornis*), bleached specimens had lower protein concentrations, by as much as 9.02 μg protein/mg lyophilized venom, than their unbleached equivalents (García-Arredondo et al., 2011; Hernández-Elizárraga et al., 2019; Olguín-López et al., 2019). Regardless of the direction of the change in the protein concentration, the overall profile of the venoms amongst all species was shown to be impacted by bleaching (García-Arredondo et al., 2011; Hoepner et al., 2019; Olguín-López et al., 2019). This was evidenced with both one-dimensional (García-Arredondo et al., 2011; Hoepner et al., 2019; Olguín-López et al., 2019) and two-dimensional gel electrophoresis surveys (Hernández-Elizárraga et al., 2019; Olguín-López et al., 2019).

In hydrozoans, bleaching appeared to down regulate 11 and 20 proteins in *M. alcicornis* (Olguín-López et al., 2019) and *M. complanata* respectively (Hernández-Elizárraga et al., 2019). Similarly, six (Olguín-López et al., 2019) and 15 proteins were shown to present in higher levels (Hernández-Elizárraga et al., 2019). Several of these differentially expressed proteins were identified as potential toxins via mass spectrometry (Hernández-Elizárraga et al., 2019; Olguín-López et al., 2019). In both hydrozoan species, Actitoxins and Phospholipase A2 (PLA2) toxins were shown to be among those that had increased expression (Hernández-Elizárraga et al., 2019; Olguín-López et al., 2019). Bleached *M. complanata* venom was also shown to have increased expressions of an echotoxin and a metalloprotease protein, and reduced levels of a PLA2-like toxin (Hernández-Elizárraga et al., 2019). A type of metalloprotease protein was shown to decrease in *M. alcicornis* however (Olguín-López et al., 2019). Together, these findings highlight that bleaching may not only limit a cnidarians' ability to produce venom, but also, have the capacity to alter the chemical make-up of the cnidarians venoms itself.

3.3. *Effects on venom toxicity*

Coinciding with the changes to the venom profiles and protein concentration, bleaching has been shown to influence venom toxicity, specifically lethality towards *Artemia* sp. (brine shrimp) and cytotoxicity of cnidarian venom (García-Arredondo et al., 2011; Hernández-Elizárraga et al., 2019; Hoepner et al., 2019; Olguín-López et al., 2019). Bleaching appeared to induce a significant, though temporary, decrease in lethality of in *E. quadricolor* (Actiniaria) venom to *Artemia* sp. in as little as four weeks. Despite continued prolonged bleaching, toxicity began to normalize to pre-bleaching levels by week 13 (Hoepner et al., 2019).

Bleaching has also been shown to impact on the cytotoxicity, inferred by hemolytic, PLA2 and caseinolytic activity of cnidarian venom (García-Arredondo et al., 2011; Hernández-Elizárraga et al., 2019; Hoepner et al., 2019; Olguín-López et al., 2019). Hemolytic toxicity assays on the venom from *M. alicornis* (Hydrozoa) demonstrated that effects of bleaching ranged from negligible (Olguín-López et al., 2019) to a significant decrease (García-Arredondo et al., 2011). In *M. complanta* (Hydrozoa) however, both significant increases (Hernández-Elizárraga et al., 2019) and decreases (García-Arredondo et al., 2011) of hemolytic activity have been observed after bleaching. Curiously, in both instances where hemolytic activity was shown to decrease, the hydrozoans were bleached with temperature manipulation in the laboratory (García-Arredondo et al., 2011), unlike the hydrozoans that naturally bleached and were collected *in situ* (García-Arredondo et al., 2011; Olguín-López et al., 2019). Conversely, artificially induced bleaching a laboratory setting, via light deprivation, resulted in a significant increase in hemolytic activity of venom from sea anemone *E. quadricolour* (Hoepner et al., 2019).

The influence of bleaching on a venom's PLA2 activity varied significantly between species. Whilst there is no evidence to suggest that the PLA2 activity of *M. alicornis* is impacted by bleaching (García-Arredondo et al., 2011; Olguín-López et al., 2019), in the case of *M. complanta* however, it was shown to be significantly reduced (García-Arredondo et al., 2011; Hernández-Elizárraga et al., 2019). Finally, caseinolytic activity also seems to be unaffected, at least in the single Hydrozoan species investigated (Olguín-López et al., 2019). Thus, while there is evidence to show that bleaching may impact the toxicity of cnidarian venom, further research is needed to better understand the varied results.

4. Possible factors driving these changes

There are several scenarios which impact the cnidom or venom of bleached stressed cnidarians. Firstly is the possibility that the energy deficit left by bleaching may compromise the cnidarians ability to adequately maintain healthy rates of cnidogenesis (cnidae production) and venom synthesis. Under this scenario, some cnidarians may seek to compensate for this energy deficit by increasing heterotrophic feeding. To facilitate this, some cnidarians may elect to adapt their cnidom and venom accordingly, and therefore this may be a second way in which a cnidarians' venom ecology may change in response to bleaching. Conversely, there is the possibility that some cnidarians may invest in increased defense mechanisms in an attempt to protect themselves during vulnerable periods of bleaching.

4.1. *Energy deficit*

The metabolic cost of venom production is highly debated (Morgenstern and King, 2013; Pintor et al., 2010; Smith et al., 2014). Metabolic rates have been shown to increase significantly in snakes and scorpions in the 3–8 days immediately after venom extraction (McCue, 2006; Nisani et al., 2007, 2012). Such increases in metabolism (McCue, 2006; Nisani et al., 2007, 2012), along with the potential for these high metabolic rates to be sustained over the full regenerative period have led to the belief that venom production is energetically costly (Evans et al., 2019). Conversely, the results from other studies suggest that at least in the case of snakes, the costs of venom production are inconsequential, particularly when depleted at ecological relevant levels and compared to other biological processes such as digestion and shedding (Pintor et al., 2010; Smith et al., 2014). Although the metabolic cost of venom replenishment may be disputed, it is apparent that venom production does come at some cost to the animal. However, applying these ideas to cnidarians is problematic, as not only is the venom replaced, but also the venom delivery system. As such, little is known about the metabolic costs of replenishing venom in cnidarians.

Cnidocysts are single use, and once deployed, the cnidocytes are unable to secrete a new cnidocyst and are consequently broken down and replaced (Tardent, 1995). Complete cnidae replenishment is predicted to take between 5-6 days and 7–9 days in *Anemonia sulcata* (Actinaria) (Schmidt, 1982), and *Hydra attenuata* (Hydrozoa) (Bode and Flick, 1976), respectively. As up to 46% of all cells within cnidarians, such as *H. attenuata*, may be either mature or developing cnidocytes (Bode et al., 1973), there is an almost constant production of cnidocytes (Tardent, 1995). The replenishment of cnidocysts (and venom) is hypothesized to come at a significant metabolic cost (Fautin, 2009; Sachkova et al., 2020). The high metabolic costs of cnidae production has been demonstrated in *Nematostella vectnsis* (Actiniaria) as a rapid increase in the expression of genes associated with venom toxins and nematocyst structure, positively correlated to increased respiration rates over a 5 h period (Sachkova et al., 2020). These results suggest that the replacement of venoms and also their delivery systems come at a significant energetic cost to the cnidarian. Thus, it is likely that cnidarians direct a considerable amount of energy towards maintaining cnidae and venom levels.

As bleaching causes cnidarians to lose a considerable amount of their daily energy input (Gundlach and Watson, 2019; Morris et al., 2019), it is not inconceivable that bleaching may leave cnidarians without sufficient energy required to adequately synthesize and maintain their cnidae and venom stores. This appears to be the case in *Exaiptasia diaphana* (Actiniaria) where bleaching led to a significant reduction in the percentage of penetrative nematocysts within the cnidom, and an increase in spirocysts (Gundlach and Watson, 2019). Although it is yet to be confirmed, it is believed that spirocysts do not contain venom (Ashwood et al., 2021a; Fautin, 2009; Mariscal, 1974, 1984), and may therefore be metabolically cheaper than penetrative venom-filled nematocysts (Gundlach and Watson, 2019). This hypothesis supports the findings here whereby, the reduced energy levels caused by bleaching may not have been sufficient for the sea anemone to continue to maintain optimal nematocyst levels, nor optimal sizes, hence the change in cnidom and reduced sizes seen (Gundlach and Watson, 2019). Interestingly, when bleached sea anemones were supplemented with food and nutrients, the size of cnidae and the overall composition of the cnidom became comparable to their symbiotic counterparts (Gundlach and Watson, 2019).

The energy deficiency caused by the absence of photosymbionts, coupled with the theorized high costs of venom production may have accounted to the decreased volume of venom produced by *Entacmaea quadricolor* (Actiniaria) (Hoepner et al., 2019). Despite this study reporting a total increase in cnidae, these were not classified, and as Gundlach and Watson (2019) suggested, bleached cnidarians may increase the percentage of spirocysts within their cnidom. If spirocysts are indeed non-venomous as speculated, this may account for increased density of cnidae and decreased venom reported by Hoepner et al. (2019).

In addition to symbiotic state, the feeding regime (and inadvertently energy uptake) has also been shown to impact on the characteristics and functionality of the cnidom (Greenwood et al., 2003; Gundlach and Watson, 2019). Amongst symbiotic sea anemones (*E. diaphana*), those provided with *Artemia* sp. nauplii only, had significantly more p-mastigophores within their cnidom than conspecifics that were either starved or supplemented with nutrients only (Gundlach and Watson 2019). Counterintuitively, when symbiotic sea anemones were provided with both *Artemia* sp. nauplii and amino acids, they were found to have significantly fewer p-mastigophores within their cnidom (Gundlach and Watson, 2019). The benefits of food and nutrient availability were most evident in bleached sea anemones however, where those given the maximum diet (nauplii and nutrients supplements) had a significantly greater proportion of p-mastigophores (Gundlach and Watson, 2019). In addition to influencing the percentage of nematocysts within a cnidom, food availability has also been shown to impact on the ability of nematocysts, isolated from zooxanthellate sea anemone *Calliactis tricolor,* to readily discharge (Greenwood et al., 2003). In this study, it was demonstrated that nematocysts collected from sea anemones that were fed brine shrimp daily for 12 weeks, discharged significantly more than nematocysts collected from sea anemones with increased intervals between feeding over the same period (Greenwood et al., 2003). Together, these findings suggest that the cnidom may be influenced by the amount of available energy, whether by symbionts or available food, and that without the energy normally provided by their photosynthetic symbionts, the cnidarian venom systems may become compromised.

4.2. *Compensatory heterotrophic feeding*

A key facet of cnidarian venom ecology is the important role that many cnidae and their associated venoms play in prey capture and digestion. If the nutritional state becomes compromised, some cnidarians have been shown to respond by increasing the number of nematocysts within their arsenal (Flechtner and Lesh-Laurie, 1984). This has been shown in *Hydra oligactis* (Hydrozoa), where the number of mature and developing nematocysts increased when *H. oligactis* were starved over 15 days (Flechtner and Lesh-Laurie, 1984). When food was reintroduced, the number of mature nematocysts began to decrease (Flechtner and Lesh-Laurie, 1984). This demonstrates that some cnidarians elect and have the capacity to, invest in their cnidom in an attempt to increase their prey capture capabilities as required.

In the absence of photo-symbionts, some cnidarians may become more reliant on heterotrophic feeding and therefore may also invest increased energy into enhancing prey capture capabilities. Heterotrophic feeding in some cnidarians has been shown to increase when photosynthesis is compromised, either through reduced light availability or bleaching (Anthony and Fabricius, 2000; Grottoli et al., 2006). Compensatory heterotrophic feeding upon zooplankton may provide up to 100% of corals energy budget (Grottoli et al., 2006). As nematocysts are an integral part of a cnidarians' ability to capture prey, a successful transition to heterotrophy may be achieved by increasing number of nematocysts (Koch, 2014).

The state of heterotrophy appears to influence the cnidom of *Anthopleura elegantissima* (Actiniaria) (Hiebert and Bingham, 2012). This sea anemone is found to occur naturally in both symbiotic and asymbiotic states with zooxanthellae and zoochlorellae (microscopic green algae, Genus: *Chlorella*) (Hiebert and Bingham, 2012). Asymbiotic *A. elegantissima* have been shown to have larger nematocysts than polyps in a symbiotic relationship with zoochlorellae (Hiebert and Bingham, 2012). Asymbiotic individuals also tended to have longer spirocysts and greater densities of penetrative basitrich nematocysts (Hiebert and Bingham, 2012), suggesting that in the absence of photo-symbionts, this species invests in nematocysts that will aid heterotrophic feeding.

Curiously, bleaching also appears to impact on one of the mechanoreceptive mechanisms, involved in the discharge of anthozoan cnidae discharge (Gundlach, 2018). In addition to cnidocils (the mechanoreceptors that are a direct feature of cnidocytes (Slautterback, 1967)), anthozoan tentacles are also equipped with hair bundles (formations of interconnected cilia that arise from multiple sensory epithelial cells surrounding the cnidocytes) (Anderson and Bouchard, 2009; Watson and Mire, 2004). Bleaching has been shown to increase both the abundance and length of these hair bundles within sea anemones (Gundlach, 2018). It is theorized that this plasticity may be an attempt to increase the sensitivity of cnidae to discharge, ultimately enhancing the likelihood of capturing prey (Gundlach, 2018).

In addition to the alterations to a cnidarians' cnidom and mechanoreceptors, some cnidarians may also change the composition and toxicity of their venom in an effort to increase heterotrophic feeding (Hernández-Elizárraga et al., 2019). Together, the cnidom and venom plasticity exhibited by some cnidarians in response to prey type, satiation and symbiotic state support the hypothesis that a switch to heterotrophy may lead some cnidarians to change their cnidom and venom accordingly. Further research is required to test if this plasticity occurs within bleached symbiotic cnidarians.

4.3. *Increased defensive measures*

Cnidarians are particularly vulnerable to predation during periods of bleaching (Slattery and Paul, 2008). There have been instances when corallivory for example has been shown to increase on stressed cnidarians (McIlwain and Jones, 1997; Slattery and Paul, 2008; Tsang and Ang, 2015). There is the possibility that some cnidarians may direct their energy reserves towards defense during such a vulnerable time (Slattery and Paul, 2008). It has been shown that anthozoans are able to increase the number of penetrative mastigophores in their arsenal when they are threatened (Gochfeld, 2004; Jennings, 2014).

Although studies within Cnidaria are lacking, predation has been shown to influence the venom of other taxa (Gangur et al., 2017). The composition of scorpion venom for example has been shown to change in response to increased predator exposure (Gangur et al., 2017). Perceived threats of predation during bleaching may explain the differences in haemolytic activity that was seen between wild-bleached and laboratory-bleached *M. complanata* (García-Arredondo et al., 2011; Hernández-Elizárraga et al., 2019). Haemolytic activity is possibly used for defense, as it was seen to increase in bleached Hydrozoans exposed to predators in the wild (Hernández-Elizárraga et al., 2019), but not in those devoid of predatory stress in the laboratory (García-Arredondo et al., 2011). Similar differences in haemolytic activity between long-term laboratory (1 year) and wild *Stylophora pistillata* (Scleractinia) specimens have previously been attributed to differing levels of predation pressure and prey availability (Ben-Ari et al., 2018). While differences in predator exposure may have had some effect, it is unlikely to fully explain the decrease, as in the case of García-Arredondo et al. (2011), specimens were collected and held for one week prior to experimentation. Bleaching therefore is likely the driving factor for this change in toxicity.

Antagonistic encounters with competitors may also cause some anthozoans to develop specialized tentacles, such as, catch (Actiniaria), sweeper (Scleractinia) or bulbous (Corallimorpharia) tentacles

(Langmead and Chadwick-Furman, 1999; Williams, 1991). This transformation includes significant alterations to the cnidom (Langmead and Chadwick-Furman, 1999; Miles, 1991), and venom toxicity (Yosef et al., 2020). Additionally, once the perceived threat has subsided, the animals may revert their tentacles back to their original feeding tentacle state (Williams, 1991). It is possible that bleached cnidarians, which have increased predation pressure, may respond by altering their cnidom accordingly.

To date, no study has assessed the plasticity of the cnidom of cnidarians in an asymbiotic or bleached state when also subject to predation pressures. Regretfully, studies that found the extent of corallivory increased on stressed corals (McIlwain and Jones, 1997; Tsang and Ang, 2015), did not assess the cnidom. Additionally, such studies, which ranged from 12 h (Tsang and Ang, 2015) to five days (McIlwain and Jones, 1997), may not have been long enough to allow for changes of the cnidom to be initiated. This may be because it takes 5–9 days to create new nematocysts (Bode and Flick, 1976; Schmidt, 1982), therefore these short-term studies may not have allowed the cnidarians adequate time to increase their defenses. Had these studies run longer, perhaps corallivory may have decreased over time.

When the cnidom of otherwise healthy *Porites compressa* (Scleractinaria) was assessed 11 days after predation stress, significant differences in the cnidom were evident (Gochfeld, 2004). Increased mastigophore density of stressed corals coincided with an increase in feeding preference of *Chaetodon multicinctus* (butterflyfish) towards un-grazed corals (Gochfeld, 2004). This suggests that predated corals had successfully been able to increase their defense mechanisms over the eleven days following first exposure to a predation (Gochfeld, 2004). Together, this supports the hypotheses that the cnidarians may opt to invest in predatory defenses during periods of vulnerability such as bleaching events.

5. Future research

Research on the venom ecology of photo-symbiotic cnidarians' is complex. Not only do full considerations need to be made when selecting the model cnidarian species, but it is also important to identify the symbiont type and both the normal cnidom and venom profiles for the respective cnidarian species. Additionally, the method for, and confirmation of bleaching, as well as animal handling methods should also be carefully selected. This is to both minimize any confounding factors that may indirectly influence results, but also to increase the comparability between studies moving forward.

5.1. Model organism

Factors such as genetics, environment, and bleaching history each have the capacity to cause significant variability in the tolerance and response of cnidarians to bleaching both amongst individuals and intracolonially (Baird et al., 2009; Gillette, 2012; Kemp et al., 2014; Penin et al., 2007; Schweinsberg et al., 2015; Thompson and Van Woesik, 2009). In addition, many of these same factors may also impact on various aspects of a cnidarians' venom ecology. In an attempt to minimize the potential indirect impacts of such confounding factors, where possible, future studies would benefit by conducting studies on species where large numbers of genetically identical clonal individuals via capitalizing on asexual reproduction and/or fragmentation. As such, *Aiptaisia* sp. (Actiniaria), *Cassiopea* sp. (Scyphozoa) and corallimorpharians are examples of species that may be suitable model organisms in future studies. Alternatively, in the event that this is not practicable, it is recommended that a minimum of five genotypes should be used (Grottoli et al., 2020).

In addition to the ease of establishing and maintaining clonal populations of *Aiptasia* sp, there are other significant benefits of selecting members of this genus as a model for bleaching studies. Firstly, the genome of *Aiptasia* sp. strain CC7 has been successfully sequenced and assembled (Baumgarten et al., 2015). While there is considerable uncertainly around the taxonomical status of species within this genus, including the status of *Exaiptasia* sp. (Grajales and Rodríguez, 2013, 2019), having a genome for at least one known strain is a significant advantage which may allow for detailed identification of transcriptional changes associated with venom production. Further to this, researchers have also successfully been able to add fluorescent proteins, mRNA and DNA to gametes derived by CC7 (male) and F003 (female) strains, thereby allowing researchers the ability to manipulate gene expressions in *Aiptasia* sp. (Jones et al., 2018). Such technology has the potential to allow new ways of investigating how bleaching may impact on processes such as cnidogenesis, which are an integral part of a cnidarian's venom ecology.

It should be noted however, that as genomic and transcriptomic technology advances, other photosymbiotic cnidarians are becoming increasingly useful for studies in this field (Macrander et al., 2015; Madio et al., 2017; Ohdera et al., 2019; Richier et al., 2008; Sachkova et al., 2020). For example, the identification of 97 venom-encoding genes within *Cassiopea xamachana* (Ohdera et al., 2019), may now allow for differences in toxin expressions to be assessed and compared between bleached and unbleached individuals of this species.

5.2. Symbiont

Due to the wide diversity in morphology, physiology, biochemistry, and behavior of *Symbiodinium* sp., species within Symbiodinium are currently divided into nine clades (A-I) (LaJeunesse et al., 2018), six of which (A-F), have been found in symbiosis with cnidarians (Fournier, 2013), with the majority of species studied found to simultaneously host two or more clades (Silverstein et al., 2012). Much like their cnidarian hosts, different clades of *Symbiodinium* have different thermotolerances and influence how a cnidarian may respond to the threat of bleaching (Abrego et al., 2008; Morgans et al., 2020; Pernice et al., 2015; Quigley et al., 2018). Similarly, fine-scale differences in the resources translocated to the cnidarian have been found between *Symbiodinium* clades (Lin et al., 2019; Pernice et al., 2015). Indeed, changes in symbiont type have been shown to alter the metabolic performance of cnidarians (Lin et al., 2019), and it remains to be seen if this in turn may impact on cnidogenesis or venom composition. As many cnidarians' have the capacity to discriminately swap between different symbiont species in response to changes within their environment (Jones et al., 2008; Morgans et al., 2020; Quigley et al., 2018), it is highly recommended that for all bleaching studies, the *Symbiodinium* present should be identified to the highest resolution possible (Grottoli et al., 2020; McLachlan et al., 2020).

5.3. Cnidae & venom

When investigating the impacts of any stressor on a cnidarians' venom ecology it is important that it is approached holistically. Both the cnidae and the venom are of equal importance to the equation, and both have the potential to be impacted independently to one another. This is evidenced through not only the plastic responses shown by cnidae and venom, change to the venom profile in the absence of cnidae change (Underwood and Seymour, 2007), but also reductions in toxicity despite an increase in the overall cnidom (Hoepner et al., 2019).

As such, it is important to identify all the cnidae present for the species. Within the literature however, one will quickly see there have been numerous modifications to the systems used to classify cnidae over the years (Cutress, 1955; England, 1991; Mariscal, 1974; Östman, 2000; Rifkin, 1996; Weill, 1929). As such, the nomenclature is complex, with different systems sharing terminologies, but often with differences in their definitions (Cutress, 1955; England, 1991; Mariscal, 1974; Östman, 2000; Rifkin, 1996; Weill, 1929). Consider basitrichs for example, they have been defined as both having spines only at the base, and entire length of their tubule (Cutress, 1955; Östman, 2000). Regardless, when identifying cnidae it is important to firstly provide details as to which classification system was used, but also to provide photos, to avoid confusion that may arise due to the discrepancies or misinterpretation in the terminology.

5.4. Bleaching methods

Manipulation of factors such as thermal stress (McLachlan et al., 2020), ultraviolet radiation (Williams and Hallock, 2004), darkness (Hoepner et al., 2019) and low salinity (Kongjandtre et al., 2022), may be used to achieve bleaching in cnidarians. More recently, serial exposures to menthol has become an increasingly popular method (Gundlach, 2018; Gundlach and Watson, 2019; Lin et al., 2019; Matthews et al., 2016; Wang et al., 2012). In addition to its high rates of bleaching success and replicability, the appeal of this method is its lack of adverse effects on cnidarian physiology, determined through respiration, metabolomics, and survival (Wang et al., 2012). It remains to be seen however whether there may be any indirect effects of menthol on a cnidarians' ability to produce cnidae or on the chemistry of the venom itself. As such, until such determinations can be made, this method should be used with caution in studies seeking to understand impacts of bleaching on venom ecology.

Diuron (DCMU; 3-(3,4-dichlorophenyl)- 1,1-dimethylurea), a common herbicide, is also often used to inhibit photosynthesis and maintain the asymbiotic state of bleached cnidarians (Matthews et al., 2016). Diuron has been shown to be toxic to cnidarians however (Howe et al., 2017; Negri et al., 2005), and should be avoided in venom ecology studies.

Regardless of the method of bleaching, it is important to confirm that significant bleaching (Grottoli et al., 2020), whether partial or complete had occurred. Common methods used are symbiont cell density counts, chlorophyll concentration and fluorescence (Grottoli et al., 2020) and also epifluorescence microscopy (Gundlach, 2018; Matthews et al., 2016). Relying on the coloration of the cnidarian alone should be avoided, as this may be misleading (Hoegh-Guldbergl and Smith, 1989).

5.5. Animal handling

As the exposure to predators and repeated physical damage has the capacity to influence both the cnidae and the venom (Gochfeld, 2004; Jennings, 2014), care must be taken during any cnidarian venom ecology study to not inadvertently induce unwanted plastic responses to either the cnidae or venom. So as to avoid potential indirect impacts, it is recommended that the handling and provocation, including that of dissections and 'milking', of any cnidarian should be kept to an absolute minimum. In instance where sampling is required to be performed over several time-points, it may be beneficial to include two sub-sets of individuals within the population; eg. one cohort that may be used for repeatedly sampling, leaving remaining individuals untouched until significant bleaching has been confirmed at termination of the treatment.

The frequency of feeding and time of sampling thereafter should also be considered. It is common practice for cnidarians, particularly sea anemone, to be starved for several days prior to venom collection (Ashwood et al., 2021a, 2021b; Madio et al., 2017; Martins et al., 2009; Rachamim et al., 2015; Thorington and Hessinger, 1988). This serves two purposes. Firstly, maximum venom yields may achieved by the potentially higher levels of venom and mature cnidae readily available within the epidermis, compared to immediately after feeding (Bode et al., 1973). This has been seen in *Hydra attenuata* where the abundance of nematocysts was shown to peak after a two day starvation period, before gradually declining (Bode et al., 1973), presumably as a result of reduced energy input. Similarly, it may take several days for a cnidarian to replenish available toxins after expenditure either by feeding or venom extraction (Madio et al., 2017). Further to this, satiation has also been shown to inhibit nematocyst discharge in sea anemones, an effect which reversed after a 72 h starvation period (Thorington et al., 2010). Finally, a starvation period my also be beneficial for studies seeking to sample genetic material, as it ensures that the gastrovascular cavity is free from food particulates that could contaminate and compromise desired samples (Martins et al., 2009).

6. Conclusion

Cnidarian bleaching and the resulting energy deficit, has been shown to lead to significant decreases in the reproduction rates, growth, and survival of cnidarians (McLachlan et al., 2020). To date, few studies have acknowledged or attempted to understand what this may mean for the production and maintenance of optimal cnidoms and venom. This is surprising given the integral part that cnidae and venom has on a cnidarians' ability to catch prey and defend themselves from predators and spatial competitors. Emerging evidence suggests that cnidae and venom are vulnerable and subject to change with bleaching (García-Arredondo et al., 2011; Gundlach and Watson, 2019; Hernández-Elizárraga et al., 2019; Hoepner et al., 2019; Olguín-López et al., 2019). As the threat of cnidarian bleaching increases, it is imperative that we seek to understand and consider these impacts, and what they will mean for their venom ecology. Without this knowledge, not only are we are unable to fully understand how cnidarians are, and will continue to be impacted by bleaching, but also how such changes may impact on the coral assemblages and reef ecosystems.

Credit author statement

Katrina L Kaposi: Conceptualization, Writing – Draft Preparation, **Robert L. Courtney**: Writing- Reviewing and Editing, **Jamie E. Seymour:** Conceptualization, Writing – Reviewing and Editing.

Ethical statement

Ethics was not required for this manuscript as no original research was conducted in the preparation of this literature review.

Declaration of interests

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.

Acknowledgments

Kaposi, K.L was supported by an Australian Postgraduate Award provided by the Australian Government and by the Joyce and George Vaughan Bequest Scholarship, awarded by James Cook University. The authors would also like to thank the reviewers for their comments and feedback which helped in improving this manuscript.

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