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Cnidarian toxins: recent evidences for potential therapeutic uses

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Abstract
Marine toxins have received global attention for their involvement in human intoxication. Many marine phyla are well adapted to produce venoms or toxins protect themselves from associated micro fauna, predators and pathogens. Despite the toxicity, some bio toxins stand as potential drug leads in human and veterinary medicine. Amongst all marine fauna, Cnidarians are well renowned for producing bioactive peptides which are used in drug development, as they harbor various biological activities; anticancer, anti-inflammatory, immunomodulatory, radical scavenging, anti-parasitic activities, etc. Particularly, this review summarizes the bioactivities recorded from Cnidarian toxins and the possibility of using them as therapeutic agents, leading to develop into commercial products in the future.

Keywords: *Cnidarian toxicity, bioactivities, therapeutic agents*

Introduction

Oceans provide a plethora of molecules with great chemical diversity and complexity. Throughout the evolution, marine animals contribute to this high chemical diversity by producing novel secondary metabolites including toxins. Toxins are substances produced naturally or artificially and have an adverse effect on some living organisms (Vasconcelos et al. 2010) or process while venoms are complex secretions with many active constituents, usually including a variety of toxins and accessory substances which facilitate the envenomation process (Turk & Kem 2009). There are several classes of marine toxins, such as saxitoxin (STX), domoic acid (DA), ciguatoxin (CTX), brevetoxin (BTX), tetrodotoxin (TTX), okadaic acid (OA), azaspiracid (AZA) and palytoxin (PLTX) groups (Vilariño et al. 2018). Many of these are reported to cause human intoxication, after consumption of contaminated seafood, skin contact with contaminated water or inhalation of toxic aerosol (Vilariño et al. 2018).

Toxins of marine invertebrates are gained special attraction in the field of drug discovery recently, due to their potential in modulating various biological properties. These toxins are highly selective and potent (R K et al. 2020). Some toxins exhibit multifunctional role, including toxicity associated with bioactivities (Trapani et al. 2016), showing green lights for the future possibility of applying them in the field of marine pharmacology.

Of all marine invertebrates who produce toxic substances, Cnidarians (Phylum Cnidaria) are ranked at the top of the hierarchy, with approximately 10,000 species world widely (Jouiaei et al. 2015). Most of these are renowned for causing envenomation hazards to humans. The majority of Cnidarians live in saltwater habitats while, approximately 40 species, mostly hydrozoans live in freshwater (Jouiaei et al. 2015). They have toxin-producing cells or glands where commonly toxic polypeptide compounds are produced and encapsulated.

As Cnidarians are the oldest extant lineage of venomous animals and the largest phylum of toxic animals, they were well studied for their importance from the ecological and economic point of view (Turk & Kem 2009). Despite the fact that the hazard of Cnidarian toxins to humans is the most evident character, these animal toxins are also considered as a potential source of natural bioactive compounds of pharmacological concern useful to develop new drugs or biomedical materials (García-Arredondo et al. 2016; Mariottini & Grice 2016, Rosa et al. 2016). The possibility of

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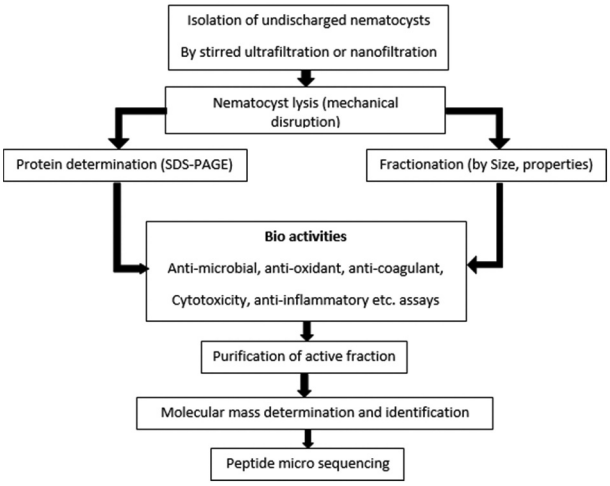

Figure 1. Schematic diagram for preparation, identification of biologically active proteins from Cnidarian crude venom.

developing these toxic molecules into drugs, still stands among attractive fields of science in the scientific community. The present review summarizes the recent evidence for beneficial bioactivities of Cnidarian toxins and the possibility of developing them into therapeutic agents, that would undoubtedly be a milestone in marine drug discovery and therapy.

Biology of Cnidarians – In brief

All the way through evolution, Cnidarians evolved a vast variety of forms and countless diversity resulting uncertain phylogeny at all its levels (Collins 2009). However, amongst all, Anthozoa, Cubozoa, Scyphozoa and Hydrozoa are the most toxic groups (Turk & Kem 2009).

Cnidarians usually have two unicellular layers (ectoderm and endoderm) separated by an extracellular matrix (mesoglea), neuromuscular systems and multiple sensory systems as common characteristic features despite the variety in size, toxicity, habitat and morphology (Technau & Steele 2012). A specialized subcellular structure called cnidae is prominent for the sudden discharge of "venoms" containing complex mixtures of bioactive compounds; biologically active molecules including 5-hydroxytryptamine, histamine, proteins such as proteases and phospholipases, and small peptides (Jouiaei et al. 2015) in order to entrap, subduing and digesting prey as well as deterring and repelling predators and competitors. On the other hand, venomous compounds exert many bioactivities such as hemolytic, cytolytic, clastogenic, enzymatic, cardiotoxic, neurotoxic and insecticidal activities (Maisano et al. 2013) and the majority of compounds are yet to be investigated.

Further, cnidae have been subdivided into three; penetrant nematocysts, the volvent spirocyst and the glutinant ptychocysts which are located in various body parts (Jouiaei et al. 2015). Cnidae are considered to be the most sophisticated lethal weapons in the animal kingdom (Tardent 1995). In addition to Cnidae, there are different types of non-nematocyst cells and unknown structures, which are used to produce a range of complex toxins that may contain surprising chemical components (Sher & Zlotkin 2009).

Cnidarian toxins: mode of secretion and delivery

Like in many other animals, Cnidarian toxins are secreted by the Golgi apparatus, however, undergo further structural modifications in the extracellular matrix before migrating to the tentacle surface (Özbek et al. 2009; Beckmann & Özbek 2012). Penetrant nematocysts inject venom into the target organism and are the most studied class of cnidae. The mechanism of cnidae discharge in response to external stimuli is still not completely understood. It is proposed that the osmotic pressure of the intracapsular fluid temporary increases as a result of cnidae exposure to the external solution and subsequent exocytosis of cations from the capsule (Jouiaei et al. 2015). The differences of the osmotic pressure between the capsule wall helps to create a threshold value of intracapsular pressure and trigger the discharge of the cnidae (Hidaka 1993). The venom which is located on the inner surface of the inverted tubule of cnidae discharges, the outside is exposed and injected into the prey (Jouiaei et al. 2015). The structure of the cnidae is important to make a successful discharge in case of entrapping, subduing and digesting prey and to repel predators and competitors. Anthozoans are getting profited by venomous apparatus located inside their body, particularly in internal and gastro dermal tissues which cause extracellular digestion and competitive interaction (Schlesinger et al. 2009). Evidently, several studies indicate the presence of toxins in mesoglea (Ovchinnikova et al. 2006) and various possible toxin containing non-nematocyst structures in body tissues of Cnidarians (Mirshamsi et al. 2017).

Extraction of Cnidarian toxins

Autolysis of nematocysts which contain venom can be proceeded by several extraction methods, slightly

different from each other (Frazão & Antunes 2016). Li et al. recently developed a fast, simplified and effective two-step method, to purify jellyfish *Cyanea nozakii* venom. In brief, the tentacles were overnight autolyzed at 4°C and stirred for 10 minutes followed by filtering through a 280 µm sieve net to remove debris (Li et al. 2011). Undischarged nematocysts can be extracted from tentacles of cnidarians using either fresh seawater, artificial seawater, filtered seawater or reverse osmosis purified water to different concentrations of saline solutions (Frazão & Antunes 2016). Other than that, sonication (Malej et al. 2012) mechanical disruption using glass beads are frequently using methods for disrupting nematocysts in order to acquire the crude venom and to suspend in a suitable buffer. Using mortar and pestle or blender increases the risk of protein degradation and contaminations compared to other mechanical techniques (Frazão & Antunes 2016).

For protein purification, identification of components of venoms; liquid chromatography, gel electrophoresis (SDS-PAGE and 2DE) are used more commonly as their effectiveness and short time duration. To detect known compounds in a venom, western blot analysis can be performed (Frazão & Antunes 2016).

Bioactivities of Cnidarian toxins

Cnidarians provide the largest source of bioactive peptides for new drug development (Liao et al. 2019). The venoms mainly contain enzymes, potent pore-forming toxins and neurotoxins (Liao et al. 2018). A large variety of peptides such as sodium and potassium channel neurotoxins, cytolysins, phospholipase A2 (PLA2), acid-sensing ion channel peptide toxins (ASICs) and other toxins are also reported from Cnidarians (Rosa et al. 2016).

Neurotoxin 2 (ATX-II), a Na + channel blocking toxin of *Anemonia sulcata* have displayed a dual role as toxin and as antibacterial activity (Trapani et al. 2014). Logashina *et al*. have reported that Ueq 12–1 which is a neurotoxin isolated from *Anemonia sulcata* and *Urticina eques* inhibits the growth of series of human pathogens; *Corynebacterium glutamicum, Staphylococcus aureus* (Logashina et al. 2017). Cytolytic actinoporins, cardio stimulatory proteins and cytolysins of sea anemones; *Heteractis magnifica and Stichodactyla mertensii* exhibited higher potential against microbial pathogens like *Staphylococcus aureus* and *Salmonella typhi* (Ghosh et al. 2011). According to Kim et al., a novel sea anemone neurotoxin, Crassicorin-I was effective against *Bacillus subtilis* at a minimal effective concentration of 11.49 l gmL^{-1}, and moderate antimicrobial potency was observed against *E. coli* and *Salmonella enterica* (Kim et al. 2017). Methanol extracts of nematocysts of *Stichodactyla mertensii* and *Stichodactyla gigantea* showed moderate effectivity against human pathogens; *Staphylococcus aureus*, *Salmonella typhi* and *Vibrio cholerae* (Thangaraj et al. 2011).

The common sea whip, *Leptogorgia virgulata* of the family Gorgoniidae (Shapo et al. 2007) has homarine and/or a homarine analog which is an active components in innate immune system. This compound inhibited the growth of *Vibrio harveyii* and *Micrococcus luteus*, indicating their antimicrobial activity (Sun et al. 2012).

Aurelin, which was isolated from mesoglea of jellyfish *Aurelia aurita* belongs to superfamily of defensins and exhibited higher activity against Gram-negative and Gram-positive bacteria (Ovchinnikova et al. 2006). Further, venom of the jellyfish *Chrysaora quinquecirrha* was moderately effective against 10 pathogens (*Escherichia coli, Vibrio cholerae, Salmonella. paratyphi, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Proteus vulgaris* and *Klebsiella oxytoca*). *Salmonella paratyphi* is the most sensitive pathogen for the venom (Suganthi & Bragadeeswaran 2012).

Neurotoxins of jellyfish *Gonionemus vertens* are reported with the ability to modulate the adhesion of macrophages. *Pelagia noctiluca* crude venom and its components exhibit cytotoxic and antiproliferative activities preferentially on tumor cell lines (Ayed et al. 2012). Venom isolated from *Chironex fleckeri* tentacles which cause excruciating pain and local tissue damage, rapidly killed human cells and similar results were obtained by evaluating LDH release or ATP depletion. Interactions between jellyfish venom components and human factors can provide an entry point to exploit jellyfish venom components as new medicines accelerate drug discovery (Lau et al. 2019).

In addition, a toxic protein (CcTX-1), from the venom of *Cyanea capillata* with proven cytotoxicological effect is structurally characterized and described for the first time (Lassen et al. 2011). According to Lee et al., *Nemopilema nomurai* jellyfish venom has anticancer activity which strongly induces cytotoxicity against HepG2 cells through apoptotic cell death (Lee et al. 2017). Two low molecular weight toxins named PpV9.4 and PpV19.4 have been isolated from *Physalia physalis* venom is reported with inhibitory action of insulin-secreting activity (Diaz-Garcia et al. 2012). Further, *Palythoa caribaeorum*'s venom was investigated by Lazcano-Pérez et al. was considered as an anticancer

compound, as its major inhibitory effect was observed on the glioblastoma cell line and human lung cancer cells (Lazcano-Pérez et al. 2018). According to another study carried out by Mirshamsi *et al.*, *Cassiopea andromeda*'s crude venom selectively induced ROS mediated cytotoxicity by directly targeting mitochondria, isolated from cancer tissue of patients with breast adenocarcinomas (Mirshamsi et al. 2017).

Further to the above studies, isolation of peptides in venoms of Cnidarians is reported. The peptide isolated from venom of *Chrysaora quinquecirrha* venom exhibited effective cytotoxicity over alveolar epithelial carcinoma cell lines and cervical cancer line cells without affecting normal human lymphocytes (Balamurugan et al. 2009). It successfully worked on Ehrlich ascites carcinoma tumor model possessing significant antitumor and antioxidant activity (Balamurugan et al. 2010). *Litophyton arboretum*, a soft coral, has been tested on the cervical cancer cell lines and leukemia cancer cell lines resulting in strong anticancer activity with high safety margins (Ellithey et al. 2014).

The venom of *Pelagia noctiluca*, a jellyfish species, contains components that reduce NO, without affecting the viability of macrophages, inducing anti-inflammatory activity (Ayed et al. 2012). In another study, a protein called smP90 was isolated from *Stomolophus meleagris* observing its superoxide anion radical scavenging activity (Li et al. 2012). Besides, Homerin which is responsible for feeding deterrent and fight response was extracted from tentacles of *A. sulcata*, had shown anti-inflammatory and immunomodulatory activities (Aassila et al. 2013). The venom of jellyfish, *Chrysaora quinquecirrha* have shown significant immunomodulatory activity in higher concentrations (Suganthi & Bragadeeswaran 2012).

In addition, crude venom of *Pelagia noctiluca* showed *in vivo* analgesic and *in vitro* plasma anti-butyrylcholinestrasic activities without inducing acute toxicity (Ayed et al. 2012). The crude venom of moon jellyfish *Aurelia aurita* is known to have different peptides show strong anticoagulant activity *in vitro* (Rastogi et al. 2012).

According to a recent study of Li et al. (2012) a novel anti-oxidant protein was isolated from nematocyst extract of jellyfish *Stomolophus meleagris* that exhibited strong superoxide anion scavenging activity. Venom of *Palythoa caribaeorum* is contained peptides that show antiparasitic activity against *Giardia intestinalis* (Lazcano-Pérez et al. 2018). Three different sea anemone toxins sticholysine I and II from *Stichodactyla helianthus* and equinatoxin II from *Actinia equina* were all found to specifically kill *Giardia duodenalis* and it can improve by combining with anti-Giardia antibodies (Tejuca et al. 1999).

Although hundreds of bioactive compounds that have a potential drug lead were recorded recently from Cnidarian toxins, only one peptide (ShK-186) known as dalazatide has reached to the pharmaceutical market, passing every stage in the pathway of drug development (Liao et al. 2018). This is used to treat autoimmune diseases, including neuroinflammatory diseases by targeting Kv1.3 channels (Wang et al. 2020). This confirms the higher degree of success in bioprospecting the cnidarian neurotoxic peptide derivatives into treatments for neurological disorders. Recently, Liao et al. reported a novel toxic peptide (PpVα) from *Protopalythoa variabilis* that suppresses the 6-hydroxydopamine (6-OHDA) induced neurotoxicity on the locomotive behavior of zebrafish and prevented the 6-OHDA-induced excessive ROS generation (Liao et al. 2019). Further, a novel Kunitz-like peptide (PcKuz3) has been identified from *Palythoa caribaeorum*, as a neuroprotective agent providing an opportunity to develop a treatment for neurodegenerative diseases (Liao et al. 2019). According to a latest research, another type of kunitz peptide was reported that exhibit neuroprotective activity against 6-hydroxydopamine (Kvetkina et al. 2020).

Challenges and limitation of utilizing Cnidarian toxins

According to Tox-Prot, an animal venom annotation database, only 273 toxins have been recorded by 2020, from the whole phylum Cnidaria which includes more than 13,000 of species. Within that, very limited number of toxin molecules have completed preclinical stages (A M et al. 2020). It further warrants potential of drug screening towards the discovery of much-needed therapeutics. Most of the animal peptides and proteins derived from toxins are natural ligands of membrane ion channels or receptors with prominent specificity and high potency that still have many challenges in bioprospecting. This may be due to the difficulties in sampling, the infrequent availability of bioactive compounds, the small amounts of extracts and the huge structural diversity of marine compounds (Leone et al. 2013). Obtaining pure samples with a sufficient quantity and high specificity on its molecular targets are other major concerns. They can interfere the sensitivity and accuracy of analysis assays which are performed at the whole animal, cell-based or molecular levels in classical phenotypic

drug discovery as well as target-based drug discovery. Further, poor solubility, short serum half-life, poor oral bioavailability, low membrane permeability, instability during storage and transport and potential immunogenicity are some confronting difficulties in the path of therapeutic development (Chen et al. 2018). However, the development and improvement of more advanced techniques, technologies, and computation applied to biology will foster productive medicinal products from largely unexplored areas in upcoming years.

Conclusion

Animals produce natural toxins in order to utilize them for defense or predatory purposes. Recently, a long lasting interest on marine toxins has risen in the field of drug discovery and development which has proven a wide spectrum of pharmacological and medical potentials. However, with respect to other marine toxins, Cnidarian toxins are not adequately investigated for bioactive properties except neurotoxins that are being tested in various therapeutic applications in nervous system. Screening of these toxins for variety of bioactivities and evaluating these activity on different *in vitro*, *ex vivo* and *in vivo* models is highly recommended in developing them into potential drugs. The potential therapeutic value of these Cnidarian toxins, thus needs to be a major focus in drug discovery and therapy.

Disclosure statement

The authors have no conflicts of interests.

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