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Review Article

COELENTERATE TOXINS, ITS PHARMACEUTICAL AND THERAPEUTIC EFFECTS

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ABSTRACT

Present review article emphasizes species specific coelenterate toxins, its pharmaceutical and therapeutic effects. Most of the coelenterates inflict venom accidently by using nematocysts found on arms. These animals very quickly do massive and multiple inflictions of venom which causes cardiotoxicity that leads to the death of human beings. Coelenterate venom toxin groups differ in their composition and show diverse biological activity i.e. cytolytic or neurotoxic, hemolytic, anti-parasitic activity, α-amylase inhibitor activity, and analgesic activity anti-cancerous and antitumor activity, anti-inflammatory and antimicrobial activity. Coelenterate venom initiates toxic and immunological reactions exert their effects by modifying the properties of the ion channels involved in action potential generation in nerve, heart, and skeletal muscles. This article suggests available information, on coelenterate toxins could be used to develop potential therapeutic interventions for various human diseases and disorders.

Keywords: Coelenterate toxins, Ion channels, Venoms biological, Pharmaceutical and therapeutic effects

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INTRODUCTION

Coelenterate venom toxins were evolved during very long evolutionary period. The origin of venom shows biological relevance as it was evolved in response to predator attack and for feeding to immobilize or kill the prey. In coelenterates defense organs were evolved due to environmental adaptations and survival competition during long evolutionary selection and mutational mechanisms. Both production of venom, its infliction, intelligence, and genetic coherence seems integration of genetic system and environmental change [1]. Coelenterates have been divided in five main classes of toxic marine animals: Anthozoa, Cubozoa, Scyphozoa and Hydrozoa. They are the largest and oldest phylum of toxic marine animals which use venom for their territorial protection from enemies and hunting the prey [2]. Coelenterates use toxins for prey acquisition, and to deter potential predators (with neurotoxicity and cardiotoxicity effects) and to fight territorial disputes (table 1).

Cnidarians are the oldest extant lineage of venomous animals on earth. The Anthozoa class includes sea anemones, hard corals, soft corals and sea pens. Anthozoan orders Alcyonacea and Gorgonacea exhibit by far the highest number of species yielding promising compounds [3]. Cnidrians are highly sensitive climate change i.e. corals and anemones have undergone climate-induced bleaching due to present extreme environmental conditions. Climate has largely affected the symbiotic relationships in sea anemones and photosynthetic algae (zooxanthellae) are showing whitening of their color (table 1). These environmental changes are also responsible for loss of internal food supply and reduction in health that results in the death of coelenterates [4].

Organs of defense

Cnidarians have also developed venomous apparatus nematocysts for the injection of toxins into the victim. The nematocyst is one of the most complex intracellular structures found cnidarians (sea anemones, corals, jellyfish, and hydroids) (fig. 1). This battery-like structure helps to inject the venom that initiates toxic and immunological reactions in the envenomated organism. Most cnidarian members attack/defend very fast and efficiently and cause massive envenomation in humans that result in death. Nematocyst discharge in coelenterates is related to the toxins found in cell-and tubule-walls of nematocysts including their polysialic acid (polySia) dependent target function. The nematocyst of the sea anemone *Nematostella vectensis* contain contains putative venom proteins, a metallopeptidase found in pharyngeal gland cells [5]. Venom infliction affects survival, functioning and metabolism in coelenterates animals (table 1). The nematocyst discharge process can be used in the development of nanomedical devices for cancer diagnostics and therapies [6] (table 1).

Venom composition

Cnideriantoxins comprises of large variety of polypeptide and protein toxins which contain proteinaceousandnon-proteinaceous compounds (purines, quaternary ammonium compounds, biogenic amines and betaines). Cniderian venom is rich source of peptides i.e. phopholipase A2, (EGF)-like toxin (gigantoxin I), Shk, APETx2 [7] (table 1). Most of the peptides are typically 10–60 amino acids long, and folded into well-defined secondary structures. Few of these peptides are enzymatic in nature and are major inhibitors or modulators of different ion channels and neurotransmitter receptors with high potency and selectivity. These are stabilized by multiple, highly-conserved disulfide bonds and are cysteine-stabilized toxins which exert their effects by modifying the properties of the ion channels involved in action potential generation in nerve, heart, and skeletal muscle. Sea anemone venom toxins posses three receptor sites Type I and Type III sodium channel inhibitors Phospolipase acts as Type I and Type III sodium inhibitors of both sodium and potassium voltage-gated channels [8] (table 1) (fig. 1).

Cnidarian toxins comprise a large variety of polypeptide and protein toxins (e. g. most toxins from sea anemones and jellyfish) as well as other organic compounds. Currently, around 250 of those compounds have been identified. Only few proteins have been deduced for their three-dimensional structures. The diversity of the chemical structure of these compounds is also reflected in a great variety of their action on cells and imposes path physiological effects suchcardiotonic, cardiotoxic, neurotoxic in man [9].

Cnidarians toxins

Sea anemones toxins

Sea anemone (Cnidaria, Anthozoa) venom is an important source of bioactive compounds, mainly toxins. These cause severe cardiotoxicity and results in the death of human beings [10]. Tube anemones or cerianthids, posses venom in stinging-cell rich tentacles prey and defend against predators [11]. These animals

produce venoms of exceptional molecular diversity. These venom components also show diverse pharmacological activity and amino acid sequence [12]. Sea anemones possess APETx1 and APETx2 toxin peptides, first one inhibits human potassium channels, while second one inhibits acid-sensing ion channels in sensory neurons. Gigantoxin I also acts as an epidermal growth factor (EGF)-like toxin [13]. From Sea anemones possess four different types of channels i.e. type 1 toxins to inhibit Shaker-related K_V channel currents by a "functional dyad" directly interacting with the channel pore. Similarly, α-actitoxin-Ate1a (Ate1a) selectively inhibits voltage-gated potassium channel [14]. BDS-I and II, selectively which target Kv3.4 channels (table 2) (fig. 1).

Table 1: Showing major coelenterate venoms with their major physiological effects

S. No.	Species name	Toxins	Effects	References
1.	*Chrysaorafuscescens*	Proteinases, venom allergens, C-type lectins, pore-forming toxins, glycoside hydrolases	Ion channel blockade and modulatory activities	Ponce D *et al.* 2016
2.	*Stichodactyla helianthus*	ShK	Potassium channel blocker	J. Prentis P *et al.* 2018.
3.	*Protopalythoa variabilis*	ShK/Aurelin family	Neurotoxic peptides, hemostatic and hemorrhagic toxins, pore-forming proteins,	Huang C *et al.* 2016.
4.	*Anthopleura elegantissimanot*	Actinoporins	Protease inhibitors	Tomohiro Honma *et al.* 2005.
5.	*Eisenia foetida*	Lysenin	Pore-forming toxin	Sukumwang N *et al.* 2013.
6.	*Palythoa caribaeorum*	PcShK3	Neuro-and cardio-protective	Liao Q*et al.* 2018.
7.	*Hydra magnipapillata*	Actinoporins	Haemolytic activity	Liew YJM *et al.* 2015.
8.	*Heteractis crispa*	APETx2	Acid-sensing ion channels	Kalina RS *et al.* 2020.
9.	*Bunodosomacaissarum*	BcsTx1 and BcsTx2	Potassium channel toxins	Diego J. B. Orts, *et al.* 2013
10.	*Phymanthus crucifer*	PhcrTx1	An acid-sensing ion channel (ASIC) inhibitor	Armando Alexei Rodríguez, *et al.* 2018.

Table 2: Showing major sea anemone venoms with their major physiological effects

S. No.	Species name	Peptide toxins	Biological effects	References
1.	*Actinia equina*	Ae I	Sodium channel toxins	Lin *et al.*, 1996
2.	*Anemonia erythraea*	AETX I	Cardiac channel	Shiomi *et al.*, 1997
3.	*Anemonia sulcata*	ATX Ia and Ib	sodium channel toxins	Widmer *et al.*, 1988
4.	*Anthopleura elegantissima*	ApC	Voltage-gated sodium channels	Norton, 1981
5.	*Anthopleura fuscoviridis*	AFT I and II	neurotoxins acting on voltage-gated sodium channels	Sunahara *et al.*, 1987
6.	*Anthopleura xanthogrammica*	ApA	Cardiac channel	Tanaka *et al.*, 1977
7.	*Anthopleura sp.*	Hk2a, 7a, 8a, and 16a	Cardiac channel	Wang *et al.*, 2004
8.	*Bunodosoma caissarum*	Bc III	neurotoxins acting on voltage-gated sodium channels	Malpezzi *et al.*, 1993
9.	*Bunodosoma cangicum*	Cangitoxin	neuronal sodium channels	Cunha *et al.*, 2005
10.	*Bunodosoma granulifera*	Bg II and III	3-to 5-kDa neurotoxins acting on voltage-gated sodium channels	Loret *et al.*, 1994
11.	*Condylactispassiflora*	Cp I and II	voltage-gated sodium channels	Shiomi *et al.*, 1995
12.	*Stichodactyla helianthus*	Gigantoxin II	Cardiac channel	Shiomi *et al.*, 2003
13.	*Stichodactylagigantea*	Gigantoxin II	3-to 5-kDa neurotoxins acting on voltage-gated sodium channels	Kem *et al.*, 1989
14.	*Radianthus (Heteractis) paumotensis*	Rc I	voltage-gated sodium channels	Shiomi *et al.*, 1996
15.	*Antheopsismaculata*	Am III	voltage-gated sodium channels	Honma *et al.*, 2005

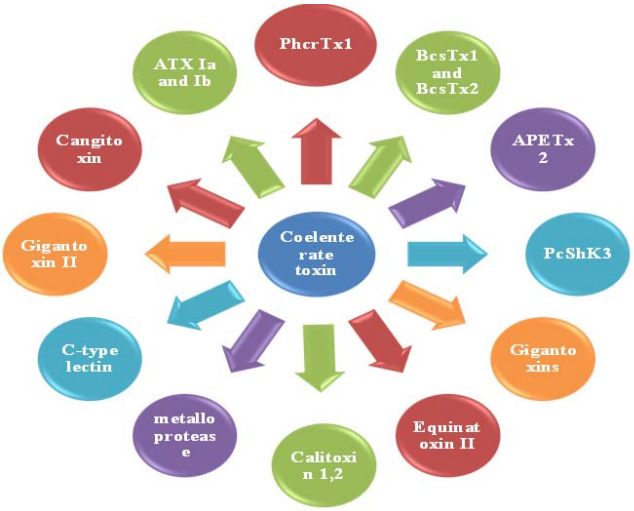

Fig. 1: Coelenterate venom toxin molecules isolated from different species

PhcrTx1 toxin characterized from the sea anemone *Phymanthus crucifer*, is ASIC inhibitor shows lower potency on Kv channels [15]. Sea anemone *Anthopleura dowii* Verrill venom contains a neurotoxins, including proteases, that act as either potassium (K^+) or sodium (Na^+) channels inhibitors [16]. These neurotoxins act upon a diverse panel of ion channels, such as voltage-gated sodium and potassium channels. These mainly target sodium channels and are modifiers of these channels [17]. These toxins target Voltage-gated Na (+) channels and are responsible for the conduction of electrical impulses in sea anemone, consist of cysteine-rich peptides capable of binding different extracellular sites of this channel protein. Four different types of neurotoxins with different structure and mode of action have been isolated from sea anemones [18] (table 2).

Sea anemone type 1 peptides known found active on Na(v)1. x channels. These peptides are 46-49 amino acid residues long contain three disulfide bonds and their molecular weights range between 3-5 Kda [19]. Sea anemone *Anthopleura maculate* contain three peptide toxins (Am I-III) with crab toxicity Type 1 sea anemone sodium channel toxins, both Am I (27 residues) and II (46 residues) are potent neurotoxins [20]. Sea anemone *Heteractis crispa* contain neurotoxin RTX-VI that modulates the voltage-gated sodium channels (Na_V). The RTX-VI molecule consists of two disulfide-linked peptide chains and is devoid of Arg13, for the Na_V channels. System ($Na_V1.2$, $Na_V1.6$) and insect ($BgNa_V1$, $VdNa_V1$) sodium channels [21]. A neurotoxin (BDS)-like antimicrobial peptides (AMPs)-Crassicorin-I and its putative homolog (Crassicorin-II) that was isolated from the pharynx extract of an anthozoan sea anemone (*Urticina crassicornis*). Crassicorin-I shows the functional linkage between AMPs and neurotoxins in a basally branching metazoan [22] (table 2).

The sea anemone *Stichodactyla haddoni* contains peptide toxins, SHTX I-III with crab-paralyzing activity, an epidermal growth factor-like peptide and SHTX IV with crab lethality. SHTX I (new toxin, 28 residues), II (analogue of SHTX I, 28 residues) and III (Kunitz-type protease inhibitor, 62 residues) are potassium channel toxins and SHTX IV (48 residues) is a member of the type 2 sea anemone sodium channel toxins [20]. Indeed, cnidarians are considered is largest phylum of toxic animals. These toxic products, particularly peptide toxins, could be used as a promising target for biomedicine research. *Stichodactyla helianthus* contains potassium channel blocker ShK its analogue ShK-186 for the treatment of autoimmune diseases [23] (table 2) (fig. 2).

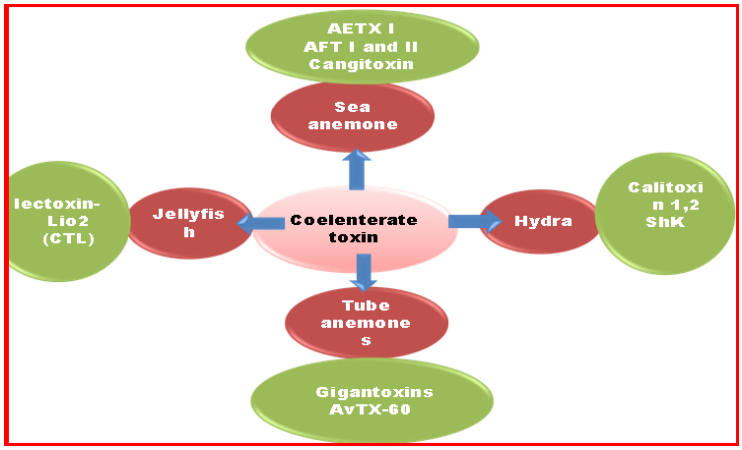

Fig. 2: Major venom toxins isolated from hydra, jelly fish, sea anemone toxins and tube anemones

Table 3: Showing major various venom toxins with their major biological effects

S. No.	Toxin type	Peptide toxins	Biological effects	References
1.	Neurotoxins	ATX-II	Slows NaC inactivation	D. Sher *et al.*, 2005
2.	Neurotoxins	ATX-III	Slows NaC inactivation	D. Sher *et al.*,2005
3.	Neurotoxins	Calitoxin 1,2	Release of neurotransmitter, possibly affecting NaC channels	D. Sher *et al.*,2005
4.	Neurotoxins	BDS-I,II	Blocks fast inactivating KC channel Kv 3.4	D. Sher *et al.*,2005
5.	Neurotoxins	ShK	Blocks voltage dependent KC channels Kv1.3 and 1.1. Isolated from homogenized bodies	D. Sher *et al.*,2005
6.	Neurotoxins	AeK	Block voltage gated KC channels	D. Sher *et al.*,2005
7.	Neurotoxins	APETx1,2	Blocks ether-a-go-go KC channels	D. Sher *et al.*,2005
8.	Cytolysins	Equinatoxin II	20 kDa, pore-former, toxic	D. Sher *et al.*,2005
9.	Cytolysins	CaTX-A	43 kDa, pore-former, toxic	D. Sher *et al.*,2005
10.	Cytolysins	AvTX-60	60 kDa, pore-former, toxic, MAC-PF domain	D. Sher *et al.*,2005
11.	Cytolysins	Hln	27 kDa, pore-former, toxic	D. Sher *et al.*,2005
12.	Phospholipases	Jellyfish Phospholipase A2	neurotoxic activity	D. Sher *et al.*,2005
13.	EGF-like toxins	Gigantoxins	3-to 5-kDa neurotoxins acting on voltage-gated sodium channels	D. Sher *et al.*,2005

Jellyfish toxins

Jellyfish are scyphozoans which possess venoms which is rich sources of toxin petides and protein. Jellyfish use stings to capture prey or deter predators. These are a major threat to human beings in coastal areas. Jellyfish *Stomolophusm eleagris* is a very dangerous animal because of its strong toxicity. The mesoglea of a scyphoid jellyfish *Aurelia aurita* contain 40-residue antimicrobial peptide, aurelin. Each year, hundreds of thousands of victims are stung by venomous jellyfish. *Nemopilema nomurai* phospholipases causes highly lethality after stinging. These toxins mainly cell membrane-and show thrombin-like activity and cause hemolysis [24]. Preproaurelin is a 84-residue signal peptide that have 22 amino acids. This peptide shows partial similarity with defensins and K+ channel-blocking toxins of sea anemones which belongs to ShKT domain family [25] (table 3).

The major components in toxins are C-type lectin, phospholipase A_2, potassium channel inhibitor, protease inhibitor, metalloprotease, hemolysin and other toxins. Presence of the compounds make sting more toxic [26] Jellyfish envenomations shows dermatological symptoms, and cause inflammation. This venom induced inflammation may be caused due inhibitory effects of matrix metalloproteinase (MMP) inhibitors for venom-induced inflammation were explored at a cellular level [27] (table 3).

Protopalythoa

Protopalythoa is a zoanthid together with marine species hydra, jellyfish, and sea anemones, composes the oldest eumetazoan phylum, i.e., the Cnidaria. These animals are highly venomous organisms that can produce deadly toxins for preying, or for territorial for defense. Zoanthid *Protopalythoa variabilis*, contain venomputative proteins from different toxin families. Most of them are neurotoxic peptides, hemostatic and hemorrhagic toxins, membrane-active (pore-forming) proteins, protease inhibitors, mixed-function venom enzymes, and auxiliary venom proteins. These toxins products belongs to ShK/Aurelin family and anthozoan toxin present in larval zebrafish [28].

Hydra toxins

Hydra is one of the evolutionary oldest animals with naturally occurring tumors. It forms a causal relationship between an environmental spirochete (Turneriella spec.) [29]. Similar hydra metalloproteinase, HMP1, and odocoryne metalloproteinase 1 (PMP1) have been also isolated from jellyfish and sea anemone toxins [30] (table 3).

Allomones

Cnidarians possessallomonal system that consists of various toxin types' neurotoxins, cytolysins and toxic phospholipapses. Mainly allomones are secreted from specialized stinging cells or nematocytes found either on arms or in other body tissues. These are used to make a defense against predators and prey capture for feeding. Feeding behavior in Hydra is maintained by receptors to GABA and glycine in the neuromuscular circuitry [31]. Hydrae also possess proteins similar to elapid-like phospholipases, CRISP proteins, Prokineticin-like polypeptides and toxic deoxyribonucleases [32]. These also possess neuropeptides in neurons of the basal disk, gastric region and tentacles [33]. Cnidarian, Hydra vulgaris contains newastacin proteinase, a hydra metalloproteinase 2 (HMP2). The mature HMP2 contains 496 amino acids and a zinc-binding motif. It shows resemblance to meprins, a subgroup of astacin metalloproteinases characteristic of the astacin family. Hydra nematocysts secrete minicollagen-1 which is a trimeric protein having cysteine-rich domains at the N and C termini [34] (fig. 2).

Toxin peptides from coelenterates

Cytolysins

Cytolysins, toxins found in sea anemone with Kunitz-type protease inhibitors activity and toxins with Phospholipase A2 activity [35] (fig. 2).

ShK

Sea anemone *Stichodactyla helianthus* possess ShK toxin a 35 residue peptide that is a potent blocker of potassium channels i.e. $K_v1.3$,K_v subtypes, such as the $K_v1.1$, and $K_v3.2$ channels [36] (fig. 2).

ShK-like2

The sea anemone *Nematostella vectensis* contain ShK-like1 peptide which has a ShKT cysteine motif. This peptide is lethal for fish larvae and packaged into nematocysts. ShK-like1 is a toxic venom component. Its paralog, ShK-like2, is a neuropeptide localized to neurons. Both peptides show similarities in their functional activities [37] (fig. 2).

PcShK3

Zoantharian PcShK3 peptide shows cardio-protective and neuroprotective activity. It contains the canonical ShK domain in its structure. Several ShK analogs or valuable variants are also characterized which are of high therapeutic value [38] (fig. 2).

APETx2

Sea anemone *Anthopleura elegantissima* contains APETx2, a peptide toxin effector of ASIC3. It contains 42-amino-acid peptide cross-linked by three disulfide bridges. APETx2 causes pain and associated to acid-sensing ion channels (ASIC) are proton-gated sodium channels [39] (Acid-sensing ion channel 3 (ASIC3) inhibitors revealed ASIC3-sustained currents' inhibition for promotion of acidosis-related pain relief [40] (fig. 2).

BcsTx1 and BcsTx2

Bunodosoma caissarum contain toxinsBcsTx1 and BcsTx2 from Saint Peter and Saint Paul Archipelago, Brazil. Sequence alignment and phylogenetic analysis shows that BcsTx1 and BcsTx2 are the newest members of the sea anemone type 1 potassium channel toxins [41] (fig. 2).

PhcrTx1

Sea anemone *Phymanthus crucifer* containPhcrTx1, a peptide toxin ASIC inhibitor. Acid-sensing ion channels (ASICs) are H+-gated Na+channels that belongs toENaC/degenerin superfamily of sodium channels. ASICs possess numerous functions such as sensory perception, synaptic plasticity, learning, memory formation, cell migration and proliferation, nociception, and neurodegenerative disorders [42] (fig. 2).

Nematogalectins

Nematogalectins are bridging proteins found in tubule cell walls of nematocysts in jellyfish and hydra. These are used for nematocyst discharge process. During the nematocyst discharge process, two properties takes place pressure threshold and elasticity which is beneficial with an impact on the construction of new nanomedical devices [43, 45] (table 4) (fig. 2).

Table 4: Showing major Jellyfish toxins venoms with their major biological effects

S. No.	Species name	Peptide toxins	Biological effects	References
1.	*R. esculentum*	C-type lectin lectoxin-Lio2 (CTL)	Hemostasis-impairing toxins	Gacesa, R. *et al.* 2016
2.	*S. malayensis*	Snaclecbothrojaracin subunit beta (BJC subunit beta)	Hemostasis-impairing toxins	Gacesa, R. *et al.* 2016
3.	*C. capillata*	metalloprotease	protease-mediated tissue damage	Wang, C. *et al.* 2019
4.	*Chironex fleckeri*	metalloprotease	protease-mediated tissue damage	Brinkman *et al.* 2011

Sticholysins

Sticholysins are the actinoporins produced by *Stichodactyla helianthus*. Three different isotoxins are known: Sticholysins I, II, and III. More especially, sticholysinsinteract with biological membranes and display lytic activity and ability to interact with cholesterol, an important lipid component of vertebrate membranes [44] (fig. 2).

Actinoporins

Actinoporins are small 18.5 kDa pore-forming toxins isolated from *H. crispa* and *Heteractis magnifica*. HALT-1 and other actinoporins have similar mechanisms of pore formation. *Hydra magnipapillata,* contain six actinoporin and HALT-1 (Hydra actinoporin-like toxin-1) shows haemolytic activity [45] (table 3). These proteins form pores in biological membranes and can work as therapeutic agents for cancer therapy**.**

Cytolytic or neurotoxic

Biological effects

Cnidarians possess nematocysts found on their tentacles, acrorhagi and acontia, and in the mucous coat that covers the animal body. Sea

anemone possesses proteins and peptides which showcytolytic or neurotoxic activity. Potency of these toxins potency varies with the structure and site of action. These different target animals, such as insects, crustaceans and vertebrates. Sea anemones toxins include voltage-gated Na^+ and K^+ channels toxins, acid-sensing ion channel toxins, Cytolysins, toxins with Kunitz-type protease inhibitors activity and toxins with Phospholipase A2 activity. Similarly, *Palythoa caribaeorum* venom toxins show cytolytic activity against U251 and SKLU-1 cancer cell lines [46] Cnidarian venoms shows cytotoxic and hemolytic effects (fig. 3).

Hemolytic activity

Sea anemone *Entacmaea quadricolor* contain venom toxins in nematocysts that show haemolytic effects. The *A. equina* mucus matrix shows hemolytic activity on rabbit erythrocytes, cytotoxic activity against the tumor cell line K562 (human erythromyeloblastoid leukemia) and antibacterial lysozyme-like activity [47] *H. crispa* contain actinoporins which show potential hemolytic activity, it is employed as an offensive and defensive chemicals by corals as an armament [34]. Actinoporin show consistent different hemolytic activity in all representatives of their group (Elena Leychenko, *et al.* 2018. Sea anemones *H. crispa* is an apore-forming toxin belongs to actinoporins that show hemolytic activity of [48]. *Stylophorapistillata* α-Pocilopotoxin-Spi1 toxin (α-PCTX-Spi1) also shows hemolytic activity (fig. 3).

Anti-parasitic activity

Sea-anemone *Stichodactyla helianthus contain* cholysin I and II from (St I and St II) and *Actinia equina* (EqtII) contain equinatoxin II. Sea-anemone also contain cytolysins which have Kunitz-type protease inhibitors activity. These toxins efficiently kill Giardia cells and show anti-parasite specificity with anti-Giardia antibodies [49] (fig. 3).

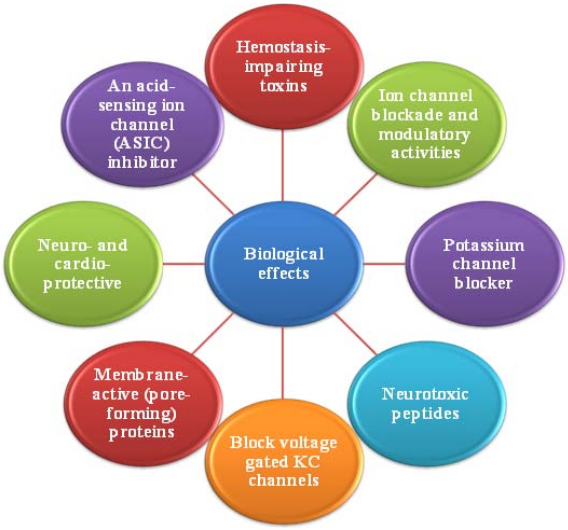

Fig. 3: Coelenterate venom toxins and its various biological activities

Antimicrobial activity

Sea anemone *B. verrucosa* contain the putative toxin, mainly metalloproteinases and neurotoxins. These also showed antimicrobial effects. Hydramacin-1 is a toxin isolated from Hydra possesses antimicrobial activity. Hydramacin-1 is potently active against Gram-positive and Gram-negative bacteria, including multi-resistant human pathogenic strains. Mason B, *et al.* 2021. Arminin 1a-C is also an antimicrobial peptide (AMP) is also isolated from metazoan marine *Hydra* [50].

α-amylase inhibitor activity

Sea anemone *Heteractismagnifica* contain magnificamide a44 amino acid peptide (4.77kDa) Da). It shows major α-amylase inhibitory activity on cytoplasmic membranes and ion channels. More especially, pancreatic α-amylase inhibitors that controls the glucose level in the blood and is highly useful in type 2 diabetes mellitus [51].

Analgesic activity

Sea anemone *Urticinagrebelnyi* contain Ugr 9-129 amino acid peptides cross-linked by two disulfide bridges shows analgesic activity [52] Ueq 12-1 is a unique peptide potentiator of the TRPA1 receptor. This is isolated from *Urticinaeques* that produces analgesic activity [53]. The cold-water sea anemone *Cnidopus japonicas* contain neurotoxins, toxin-like molecules, linear polypeptides (Cys-free), enzymes, which show analgesic effects [60] Sea anemone contains one bioactive peptide named α-AnmTxUeq 12-1 (Ueq 12-1) (fig. 3).

Anti-cancerous activity

Cnidarians possess venom toxins which show cytotoxic, hemolytic and anti-tumour effects [8, 54]. *Palythoacari baeorum* venom contains compounds which show ant-cancer activity [46] (FernandoLazcano-Pérez *et al.* 2018. *Palythoacaribaeorum* possess PLA_2 activity that showspecific cytotoxicity against U251 and SKLU-1 cancer cell lines. Actinoporins constitute a unique class of pore-forming toxins found in sea anemones that are able to bind and oligomerize in membrane. These cause cell swelling, impairment of ionic gradients and cell death. Sticholysins I and II (Sts, StI/II), areactinoporins that interact with biological membranes of cells and form pores. Sticholysins I and II also show anti-tumor effects Carlos [55]. Sea anemone *Anemonia viridis* show cytotoxic andanti-proliferative activities on cancer cell lines [56]. *Pelagianoctiluca* (*P. noctiluca*) venom shows anticancer and nitric Oxide (NO) inhibition activities. It also showed anti-proliferative activity on several cell lines, such as human bladder carcinoma (RT112), human glioblastoma (U87), and human myelogenous leukemia (K562). *P. noctiluca* venom toxins do natural inhibition of cancer cell lines [66]Sea anemones *Anemonia viridis*, contain Kunitz-type inhibitor, interact with cell membrane and bind to integrin due presence of an Arginine Glycin Aspartate (RGD) motif. This inhibitor stops new blood vessel growth or anti-angiogenesis effects [57]. Activities and Prevents HT-29 Colorectal Cancer Cell Migration [58] (fig. 3).

Nemopilema nomurai jellyfish venom (NnV) has anticancer activity. NnV strongly induced cytotoxicity of HepG2 cells through apoptotic cell death NnV inhibited the phosphorylation of PI3K, PDK1, Akt, mTOR, p70S6K, and 4EBP1, NnV exerts highly selective cytotoxicity in HepG2 cells via dual inhibition of the Akt and mTOR signaling pathways, but not in normal cells [59] (fig. 3).

Anti-angiogenesis

Sea Anemone *Anemonia viridis* contains a low molecular weight protein that shows anti-Angiogenic Activity. It also limits the proliferation of endothelial cells proliferation and angiogenesis. It

shows trypsin activity inhibition of a Kunitz-type inhibitor that interact with an integrin due to an Arginine Glycin Aspartate (RGD) motif [60]. The anti-angiotensin I converting enzyme activity of box jellyfish, *Chiropsalmus quadrigatus* Haeckel contanvenom hydrolysate. Angiotensin I converting enzyme (ACE) shows inhibitory activity [61] (fig. 3).

Antioxidant activities

The jellyfish *Rhizostoma pulmo* undergoes possess collagen peptides have significantly higher AA and possess greater protective effect against oxidative stress in HEKa than the hydrolyzed collagen peptides from vertebrates [62].

Antiviral activity

Anemonia viridis contain large number of polypeptide toxins, such as blood-depressing substances (BDS) peptides. These are 43 amino acid peptides characterized by three disulfide bonds that act as neurotoxins affecting Kv3.1, Kv3.2 and Kv3.4 channel gating kinetics. In addition, BDS-1 inactivates the Nav1.7 and Nav1.3 channels and show anti-viral effects [63] (fig. 3).

Anti-inflammatory activity

Two Kunitz-type inhibitors isolated from Sea anemones *Heteractis crispa* RG (HCRG) polypeptide subfamily have been isolated from the sea anemone *Heteractis crispa*. HCRG1 and HCRG2 possess anti-inflammatory activity, reducing tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) secretions, as well as proIL-1β expression in lipopolysaccharide (LPS)-activated macrophages [64]. Sea anemone *Heteractis crispa* contain Kunitz-type peptides, which have potassium channels blocking activity. This peptide reduced the synthesis of TNF-α, a pro-inflammatory mediator playing a leading role in the development of edema in this model [65]. Sea anemone *Metridiumsenile* contain peptide toxinsTXMs 9a-1. The transient receptor potential ankyrin-repeat 1 (TRPA1) is an important player in pain and inflammatory pathways. It shows anti-inflammatory effects in experimental mice**.** Sea anemone *Heteractis crispa* Kunitz-type peptides showed anti-inflammatory and anti-histamine effects [66]. Ueq 12-1 is a unique peptide potentiator of the TRPA1 receptor that produces anti-inflammatory effects *in vivo*. Sea anemone *Urticina eques* contain a bioactive peptide named α-AnmTxUeq 12-1. It consists of 45 amino acids including 10 cysteine residues (fig. 3).

Anti-helminthic activity

Nematostellavectensis encoding the putative nematocyst venom proteins: a metallopeptidase related to the Tolloid family and a cysteine-rich protein. These show anti-helmintic activity AnewKunitz-type protease inhibitor InhVJ from the sea anemone Heteractis crispa (Radianthus macrodactylus). The significant role of Glu45 for the orientation and stabilization of the InhVJ-trypsin complex was elucidated. P1 Thr residue instead of Lys might lead to refinement of inhibitor specificity in the direction of subfamilies of serine proteases. The absence of Kv channel and TRPV1-receptor modulation activity was confirmed by electrophysiological screening tests [67]. Sea anemone Anthopleura dowii Verrill contain venom, including proteases, neurotoxins that could act as either potassium (K+) or sodium (Na+) channels inhibitors, protease inhibitors, phospholipases A2, and other polypeptides [68]. Venomous animals from distinct phyla such as spiders, scorpions, snakes, cone snails, or sea anemones produce small toxic proteins interacting with a variety of cell targets. Their bites often cause pain [68]. One of the ways of pain generation is the activation of TRPV1 channels [70]. Sea anemone *Bunodactisverrucosa* contain putative toxins including metalloproteinases and neurotoxins which is responsible for basal metabolism and biosynthesis of antibiotics [71] (fig. 3).

Analgesic effect

Cnidarians have been known since ancient times for the painful stings they induce to humans. The effects of the stings range from skin irritation to cardiotoxicity and can result in the death of human beings [72]. The venom of sea anemone *Metridium senile* contain 35-amino acid peptideτ-AnmTXMs 9a-1 (short name Ms 9a-1) Ms 9a-1 potentiates the response of TRPA1 to endogenous agonists followed by persistent functional loss of TRPA1-expressing neurons. TRPA1 potentiating may be useful as a therapeutic approach as Ms 9a-1 produces significant analgesic and anti-inflammatory effects in mice models of pain. A new multigene HCIQ subfamily from the sea anemone *Heteractis crispa* contain Kunitz-peptides shows neuroprotective activity against 6-hydroxydopamine [73]. Sea anemone *Heteractis crispa* venoms have Kunitz-type peptides so named "analgesic cluster" of the HCGS peptide subfamily but forms a separate branch on the NJ-phylogenetic tree. rHCRG21 is the first full peptide TRPV1 inhibitor, although displaying a lower affinity for its receptor in comparison with other known ligands. rHCRG21-TRPV1 complex allow hypothesizing the existence of two feasible, intra-and extracellular, molecular mechanisms of blocking. These data provide valuable insights in the structural and functional relationships and pharmacological potential of bifunctional Kunitz-type peptides [74].

Anti-diabetic activity

Sea Anemone *Heteractis magnifica* mucus, contain Magnificamide, a β-Defensin-Like Peptidetargets, mainly on cytoplasmic membranes and ion channels. It is a rich source of pancreatic α-amylase inhibitors, which maintain the glucose level in the blood and can be used for the treatment of prediabetes and type 2 diabetes mellitus. The main function of magnificamide is the inhibition of α-amylases act as potential drug candidate for the treatment of type 2 diabetes mellitus [75] (fig. 3).

Immunomodulating activity

Sea anemone *Stichodactyla helianthus,* CCR7-effector memory T (TEM) lymphocytes. These cells express Kv1.3 potassium channels that play a major role in their activation. These act as potential immunomodulators for the treatment of autoimmune diseases. Stichodactyla helianthus is a potent blocker of Kv1.3. ShK-186, a synthetic analog of ShK, is therapeutic for autoimmune diseases [76] (fig. 3).

Mode of action

Cniderians toxins peptides acts on ligand-gated ion channels, including acid-sensing ion channel (ASIC) toxins. Thistoxins breaks glycerophospholipids, which produces lysophospholipid and fatty acids, such as the arachidonic acid. The metabolites derived from arachidonic acid (prostaglandins, thromboxanes and leukotrienes) control a variety of cellular functions, including dietary lipid catabolism, in cell membrane metabolism and inflammatory diseases. It include a large variety of proteinase enzymes, which host a metal atom to perform their catalytic activity. These toxins mainly acts on Voltage-Gated Sodium and Potassium Channel Toxins. Voltage-gated ion channels activate non-selective pores within membranes by which the ions can pass using the electrochemical gradient across the membrane itself. When this mechanism is altered, the transmission of signals through the neurons and muscles is critically changed too, which can lead to certain disorders, including paralysis. These toxins, whose molecular mass ranges from 3.5 to 6.5 kDa, are able to bind specifically with the receptor site three of the sodium channel, and regulate their functioning. By controlling the opening and closing of the sodium channel, the toxins control the electrical signals that encode and propagate vital information across long distances. The activity of the sodium channel toxins shows these toxins act as pain blockers. *Heteractiscrispa* contain Sodium channel inhibitors which was not suitable for pharmacological applications but useful to study the mechanisms of these sodium and potassium channel toxins transportation and thus to produce insecticides. *Bunodosomacaissarum* BcsTx1 and BcsTx2 secreted by sea anemone type 1 potassium channel toxins interact with voltage-gated K+channels (KV) mainly rKv1.2 over rKv1.6, hKv1.3, Shaker IR and rKv1.1 (Cnidaria, Anthozoa). Sea anemones *Heteractiscrispa* contain peptide toxins APETx-2. It also contain wo APETx-like peptides, Hcr 1b-2 and Hcr 1b-4 which interfaces with the rASIC1a channel [77]. The nematocysts of the sea anemone *Actinia bermudensis* contain peptide toxinsAbeTx1that possess a ring of basic amino acids that shows multipoint interaction for the binding of the toxin to the channel Sea anemone *Anthopleura dowii* Verrillvenom, contain proteases, neurotoxins, phospholipases A2, and other polypeptides, that act as either potassium (K^+) or sodium (Na^+) channels inhibitors [78].

Toxin bio-prospecting

Cnidarians possess an articulated cocktail of bioactive substances. 88Sea anemone-like *Anemonia viridis* contains peptide toxins arsenal is a major pool of neurotoxins. These act upon sodium and potassium channels [79]. If its RNA-Sequences and regulatory gene could be explored, than its expression effect can be measured by using simulation modeling.

Moreover, *A. viridis* toxins can be used for biotechnological applications for generation of new drugs of various biological and therapeutic activity. Similarly, *Hydra magnipapillata* and *Nematostella vectensis* belong to a prominent family cnidarians possess α-crystallin gene that could be used for biotechnological purposes [80]. The scyphomedusa *Rhizostomapulmo* is an outbreak-forming jellyfish act as vectors of bacterial pathogens [81]. Various coelenterate species possess unique mixture of toxin peptides with diverse biological and pharmacological activities [56, 82]. These toxins also act as defense molecules used by various coelenterate species [83].

CONCLUSION

Most of the coelenterates secrete venom that is a diverse arsenal of peptides and proteins used in self-defense and to immobilize the prey. These low molecular weight toxin peptides interact to voltage-gated sodium and potassium channels. These toxins fire membranes and form and accelerate active passage of ions which pass using the electrochemical gradient across the membrane itself. Coelenterate toxins show diverse biological activity such as anti-angiogenesis effects and cytolytic activity against human myelogenous leukemia and cancer cell lines. These pore-forming toxins show action much similar to actinoporins and cause hemolysis. Sea anemone *B. verrucosa* contain metalloproteinases and neurotoxins. These also show Kunitz-type protease inhibitor and pancreatic α-amylase inhibitor activity. These also show anti-pathogenic effects against microbes such as viruses, bacteria, protozoan and fungal species. These show anti-helminthic activity, analgesic effect, anti-diabetic activity and immunomodulating activity are of great of pharmacological and biotechnological interest. These could be used for the generation of new highly effective drug molecules for the treatment of various human diseases. These toxins could be used as a natural source for the development of alternative medicine.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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