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Review Article

# FISH VENOM TOXINS: NATURAL SOURCE OF PHARMACEUTICALS AND THERAPEUTIC AGENTS "PHARMACEUTICAL AND THERAPEUTIC USES OF FISH VENOM TOXINS

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**ABSTRACT**

The present review article explains fish toxins from different species with their pharmaceutical and therapeutic uses. Fish stinging is a major problem in coastal areas as it exerts severe toxic effects mainly in fishermen, locals, and tourists. Fish toxins cause severe pain that radiates up in the limbs and regional lymphatics. These also impose venular stasis, hemorrhage and make changes in the arteriolar wall diameter. Fish toxins target ion-channels, ligand-gated channels and G-protein coupled receptors present in body cells and obstructs their physiological and metabolic functions. They affect molecules that participate in signaling pathways, and cause hemolytic, cardiovascular, and make obstruction in nerve function and smooth muscle contraction. For quick neutralization, fish venom-induced effects in victim's toxin-specific antibodies are used. These quickly provide relief from pain, minimize the symptoms, and stop the immediate inflammatory reaction. Fish venom toxins are of wider biomedical applications and can be used for the preparation of immune diagnostics, bio-pesticides, anticancer agents, and analgesics by using its biological information.

**Keywords:** Fish toxin, Envenomation, Pharmaceutical activity, Bio-pesticides, Anti-venom therapy


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## INTRODUCTION

Venomous animals occur in numerous phyla and present a great diversity of Texas, which possess various toxins, with a range of targets, impose wider clinical effects with fatalities. Fish contain venom secreting cells under dorsal and pectoral spines and make stings very swiftly. In freshwater, stingrays and catfish cause clinical injuries in divers with a very similar mechanism to the poisoning and the effects of the toxins of marine species, cartilaginous stingrays *Notarygon kuhlii* and *Himantura toshi*, and the bony fishes, *Platycephalus fucus*, *Girella tricuspidata*, *Mugil cephalus*, and *Dentex tumifrons*. Its venom glands are located in the pectoral and dorsal fins. Catfish has three serrated venomous bony stings in the dorsal and pectoral fins that are used for defense against predators and are refilled by glandular tissues under the epithelium. However, some fishes do not have poisonous glands next to the sting and cause traumatic wounds without poisoning. In general, around 200 fish species were known to be venomous in the world and [1-6]. Recent estimations based on phylogeny and venom evolution around 2000 ray-finned fishes are venomous. However, despite there being over 2000 venomous fish species, piscine venoms have been relatively underrepresented in the literature thus far. Altogether, fish comprise more than half of all venomous vertebrates [7]. Interestingly, the venom apparatus and pharmacology are similar throughout most venomous fish species, despite their wide taxonomic range [7-10].

Among aquatic animals, fishes are injurious to humans and impose clinical problems. Fish envenomation is a serious problem for fishermen, surfing players, divers, and tourists [11-13]. Most of the fish toxin victims are tourists who visit oceanic sites for water surfing or go to open sea navigation at high risk of a fish sting. Sharks and rays accidentally encounter and attack swiftly. More fatal accidents happen during deep-sea diving by major carps. In freshwater, stingrays and catfish cause injuries and inflict toxins in human victims. Fish toxins show various clinical effects vary with species and venom type (fig. 1). Most important physiological effects, including local effects, are severe local pain, swelling, sweating, headache, vomiting, abdominal pain, hypertension, hypotension and blistering, bleeding, shock, paralysis, tissue necrosis and cardiac arrest, convulsions, collapse and even death (fig. 1, table 1).

Fish toxins isolated from various species show systemic effects like paralytic, hemorrhagic, neurotoxic, myotoxic, renal, and cardiac toxicity in victims (table 1). Fish toxins generate an acute inflammatory response by recruiting immune cells into peripheral tissues choreographed by chemoattractants, including lipid mediators (LTB4 and PGE2), cytokines (IL-1β and TNF-α), and chemokines (KC and MCP-1). Catfish sting is quite a menacing cause of severe tissue necrosis and poisoning [13-15]. Catfish stings showed cardiovascular and neurotoxic effects and cause severe inflammation with hemolytic, dermonecrotic, edema-promoting, vasospastic activities (table 2). Marine fishes, mainly Catfish attaches very fast and discharge venom from their dorsal and pectoral spines [15]. The fish sting apparatus is diversified specific structures and is naturally designed, adapted for fast predation and self-defense in different species [16-20].

Fish stings cause severe pain, swelling, and lymphadenopathy, followed by bullets. It also imposes secondary bacterial infections and late complications such as tenosynovitis. The general treatment for fish envenomation is primarily targeted at relieving the intense pain and involves soaking the affected area in hot water (typically 45–50 °C) for an extended time or until the pain subsides. Medical treatment includes both general and specific measures. For fast recovery, patients require appropriate treatment, which might be antibody/anti-sera. Anti-venom is highly demanded and recommended by the clinicians. However, for immune therapeutics, specific anti-venom shows an efficient intervention for protecting humanity. It can neutralize the effect of venom toxins inside the tissues.

### Source of information and search strategy for identifying relevant studies

For making a comprehensive research review of the subject, we performed searches using terms such as medical subject headings (MeSH) and key text words, such as "fish venom and toxins," "biological and pharmaceutical effects", "mode of action,", "drug development" "anti-venom therapy" published till 2019. Thus, the abstracts of published studies with relevant information on the fish toxin information centers were identified. These terms were used individually and in combination to ensure an extensive literature search. For updating the subject and incorporation of recent knowledge, relevant articles were selected and collated based on the broader objective of the review. This was achieved

by searching databases, including SCOPUS, Web of Science, and EMBASE, Pubmed, Swissprot, Google searches" From this common methodology, discoveries and findings were identified and summarized in this final review.

**Venom composition**

The fish toxins range from 50 to 800 kDa molecular weight. Fish venom contains proteinaceous and non-proteinaceous toxins. Proteins include hyaluronidase, pain-producing factor, capillary permeability factor, and species-specific toxic factors. Proteinaceous components found in the fish venom show nociceptive activity largely occurs via a non-opiate mechanism. These components are highly active toxic agents and generate pathophysiological symptoms. These are biologically important compounds/components that showed cardiovascular, neuromuscular, cytotoxic, hemolytic inflammatory, enzymatic, nociceptive, immunomodulatory, antimicrobial, anticancerous pharmacological activities [21, 22] (tables 1 and 2). Some important clades of venomous fish such as Chimaera, Rays, Armored catfish, Sharks, Siluroidei catfish Scorpionfish, stonefish belong to different taxon and secrete major toxins with different multiple biological activities from their venom glands (table 3).

Catfish *C. spixii* venom contains diverse structural proteins, chaperones, ion transport, carbohydrate metabolism, oxidoreductase, cell cycle, and protein binding in venom. Largely piscine venoms severely affect the cardiovascular system and neuromuscular systems. Their potent action starts the release of nitric oxide from endothelial cells, and does depolarizing action on nerve and muscle cells, smooth muscle contraction, but show different action on atria. Fish venom toxins/proteins isolated from different species show 90% homology and show similar responses on body cells and organs. No doubt fish venom toxins are of very high pharmacological importance [23] as their structural templates could be used for the development of human therapeutic drugs and biopesticides (fig. 2a and 2b) [24].

**Proteinaceous toxins**

**Peptide toxins**

Several large proteinaceous toxins, such as stonustoxin, verrucotoxin, and Sp-CTx, have been isolated from scorpionfish. Venom toxins isolated from stonefish; *Synanceia verrucosa* showed lethal, hypotensive, and cytolytic effects [25] (fig. 1). These toxins form pores in cell membranes, cause leakage of the cell sap, impose cell death by creating a cascade of reactions. Natterins, a novel family of toxins possessing kininogenase activity, have been found in the toadfish venom (table 4).

**Verrucotoxin (VTX)**

Verrucotoxin (VTX) is isolated from *S. verrucosa* venom. It is a tetrameric protein having a total mass of 322 kDa. The Verrucotoxin (VTX) is composed of two glycosylated α-subunits and two glycosylated β-subunits. It shows lethal and hemolytic activities, cause hypotension and cardiac arrest when injected into mice [26]. Verrucotoxin (VTX) exerts a negative inotropic and chronotropic effects on frog atrial heart muscle via the inhibition of Ca2+channels and the opening of K channels [27]. This toxin also acts as a β1-adrenoceptor agonist via the cAMP-PKA pathway, thereby leads to an increase in L-type Ca2+currents [28]. A second toxin was isolated from *S. verrucosa* venom and shown to be a hemolytic dimer composed of α and β subunits. This 166 kDa toxin was named neoverrucotoxin (neoVTX). It can be inhibited by anionic lipids (table 4).

**Table 1: Toxins found in fish venoms and their molecular weight and biological effects**

| Species | Toxin | MW | Biological effects | Source |
|---|---|---|---|---|
| *Notesthes robusta* | Nocitoxin | 169-174kDa | Spines are excruciatingly painful | [12] |
| *Synanceia horrida* | Trachynilysin (TLY)<br>Stonustoxin (SNTX) | 158kDa(2 subunits)<br>148kDa(2 subunits) | Reduce twitch height and increased basal tension, contractile response | [29] |
| *Synanceia verrucosa* | Verrutoxin (VTX)<br>Neoverrucotoxin (NeoVTX)<br>cardioleputin | 322kDa(4 subunits)<br>166kDa(2 subunits)<br>46kDa | Cell depolarization | [28] |
| *Scropaena plumieri* | Sp-CTx Plumieribetin SP-CL1- | 121kDa(2subunits)<br>14kDa 16-17kDa | Cell pore formation | [44] |
| *Hypodytes rubripinnis* | Karatoxin | 110kDa(2 subunits) | | [46] |
| *Trachinus draco* | Dracotoxin | 105kDa | Cell depolarization | [52] |
| *Trachinus vipera* | Trachinine | 324kDa | Cell depolarization | [53] |
| *Scatophagus argus* | SA-HT | 18kDa | Relaxtion and contractile response, postsynaptic blockage of eclectically induce twist response | [55] |
| *Thalassophryne maculosa* | TmC4-47.2 | unknown | Severe muscular blockade | [58] |
| *Thalassophryne nattereri* | Nattectin | 15kDa | Neuromuscular | [59] |
| *Cathrops spixii* | Wap65 | 54kDa | Cutaneous oedema, erythema at the wound site, pain, | [61] |
| *Plotosus canius* | Toxin-PC | 15kDa | hypertension and respiratory failure, cardiac arrest, neuromuscular blockage | [62] |
| *Synanceja horrida* | hyaluronidases * | 75kDa(2 subunits) | Severe muscular blockade | [90] |
| *Pterois volitans* | hyaluronidases | 75kDa(2 subunits) | Irregular muscular fibrillation and muscular blockade | [93] |
| *Pterois antennata* | hyaluronidases * | 75kDa(2 subunits) | Irregular muscular fibrillation and muscular blockade | [93] |
| *Pterois lunulata* | Unnamed* | 160kDa(2 subunits) | Irregular muscular fibrillation and muscular blockade | [111] |
| *Inimicus japonicus* | Unnamed* | 160kDa(2 subunits) | Causes severe and immediate local pain, sometimes followed by shock, paralysis, tissue necrosis and even death | [111] |

*Unnamed stonefish toxin-like toxin (based on similarities to SNTX and VTX).

**Stonustoxin (SNTX)**

SNTX (Stonustoxin) is a dimeric protein (Mol with 148 codes) composed of α and β subunits [29]. It's α and β subunits of shows 50% sequence identity VTX (verrucotoxin) [30]. It associates with non-covalent bonds to neoVTX and holds two subunits of SNTX (stonustoxin) together, instead of disulfide bridges, which are not glycosylated [31]. These two toxins differ in their cysteine content.

SNTX (stonustoxin) posses 15 cysteine residues, and 5 free thiol groups, which are involved in intrachain disulfide bonds [32]. This toxin demonstrates hemolytic activity in rats, guinea pig, and rabbit erythrocytes but it shows no effect against human and mouse erythrocytes [33]. In rat erythrocytes, the hemolytic activity was due to the formation of pores, approximately 3.2 mm in diameter, in their membranes [34] (fig. 1).

This hemolytic action subsequently induces platelet aggregation in whole blood from affected species. SNTX also demonstrates automatic properties and potentially lethal activity in mice at an LD50 0. 017µg/g. Toxin's cationic lysine and arginine residues play a large role in mediating both hemolytic and lethal activity [35]. This toxin shows hemolytic activity and displays a negligible effect on skeletal muscle contractility [36, 37]. It shows marked hypotension and endothelium-dependent vaso-relaxation which is mediated by the release of either endogenous nitric oxide (NO) or a NO-releasing substance [38]. This endogenous hydrogen sulfide works synergistically with NO to cause stonustoxin induced-vasodilation [39]. Monoclonal antibodies raised against SNTX are used to neutralize its effect. *S. verrucosa* venom was found to have relatively more norepinephrine when compared to *S. horrida*, but relatively less dopamine and tryptophan (table 4).

**Trachynilysin (TLY)**

Trachynilysin (TLY) is a dimeric protein isolated from *S. horrida* venom. It is composed of α (76 kDa) and β (83 kDa) subunits. It acts upon presynaptic frog motor nerve terminals and depletes small synaptic vesicles. No effect is seen on large dense-core vesicles [40]. TLY reduces the rate of contraction in frog atrial heart muscle cells due to endogenous acetylcholine release and its action on muscarinic receptors [41] (table 4). This toxin also increases the Ca2+entry in the cell and causes exocytosis of large dense-core vesicles from chromaffin cells. It takes place only when calcium is found extracellular [42]. It also imposes the formation of cationic pores in cell membranes through irreversible membrane insertion [43].

**Sp-CTx**

Sp-CTx was isolated from *S. plumieri*. It is a dimeric glycoprotein of 121 kDa. Sp-CTx shows both hemolytic activity and biphasic vasoactivity that involves NO as a mediator [44] (fig. 1). It also exerts pore formation in cell membranes similar to starfish toxins. Sp-CTx peptide shows sequence homology to neoVTX, SNTX, and the toxins from both *P. volitions* and *P. antennae*. Sp-CTx forms molecular aggregates that also decide the diameter of the pore formed by the toxin [45] (table 4).

**Table 2: Important catfish fauna which shows envenomation and toxicity in animals**

| S. No. | Common name | Scientific name | Family | Toxin group | Source |
|---|---|---|---|---|---|
| 1. | Magur | *Clarias batrachus* | Clariidae | Hemotoxic | [22] |
| 2. | Thai magur or Africon catfish | *Clarious gariepinus* | Clariidae | Hemotoxic | [22] |
| 3. | Blue catfish or Skinless catfish | *Lctalurus furcatus* | Clariidae | Hemotoxic, | [22] |
| 4. | Singhi or stinging catfish | *Heteropneustes fossilis* | Heteropneustidae | Hemotoxic | [22] |
| 5. | Butter catfish | *Ompok bimaculatus* | Siluridae | Hemotoxic | [22] |
| 6. | Sutchi catfish | *Pangasianodon hypophthalmus* | Pangasiidae | Hemotoxic | [22] |
| 7. | Pangas | *Pangasius pangasius* | Pangasiide | Hemotoxic, neurotoxic | [22] |
| 8. | Tengra | *Mystus vittatus* | Bagridae | Cytotoxic | [22] |
| 9. | Gulsa tengra | *Mystus bleekeri* | Bagridae | Cytotoxic | [22] |

**Table 3: Some important clades of venomous fish with their major toxin groups**

| Taxon | Location of the venom gland | Major Toxins and their effect | Source |
|---|---|---|---|
| Chimera (Chimaeridae) | Venomous spine in front of the dorsal fins. | Cry1Ac-Cry1Ab *chimera toxic* to lepidopteran insects | [7] |
| Shark (Scyllidae) | In chelicerae or under the carapace | Sharks accumulate dangerous levels of methylmercury | [7] |
| Rays (Batoidea) | Anterolateral glandular groove of dorsal fins | Causes increase blood flow in the superficial capillaries and cell death | [7] |
| Armored catfish | Alongside sharp bony spines on the edges of the dorsal and pectoral spine | Toxin PC, Toxin I, Toxin II, ' Lethal cytotoxic | [7] |
| Siluroidei catfish (Siluriformes) | Along the side of sharp bony spines on the edges of the dorsal and pectoral spine | Toxin PC, Toxin I, Toxin II, ides elicit a wide array of physiological | [7] |
| Fang Blennies | Anterolateral glandular groove of dorsal or anal fins | Cause toxicity via interactions with opioid receptors exerts potent hypotensive effects. | [7] |
| Toadfish(Thalassophryninae) | Anterolateral glandular groove of dorsal or anal fins | Causes ataxia in man, numbness and tingling around the mouth, lips, and limb extremities | [7] |
| Carangoid | Anterolateral glandular groove of dorsal or anal fins | *Brevetoxins* and ciguatoxins | [7] |
| Scats (Scathophagidae) | Anterolateral glandular groove in venomous dorsal or anal fins spine | Neurotoxins and cytotoxins | [7] |
| Stargazers (Uranoscopidae) | central spine with venom glands | Neurotoxins, Necrotoxins and cytotoxins, myotoxins, which damage muscles. | [7] |
| Rabbitfish (Siganidae) | Anterolateral glandular groove in venomous dorsal fins spine | Human health risk at a very lower dose | [7] |
| Surgeonfish (Acanthouridae) | Anterolateral glandular groove of dorsal fins spine | Maitotoxin (MT) | [7] |
| Weerfish (Trachinidae) | Operculum spine and anterolateral glandular groove in venomous dorsal or anal fins spine | Dracotoxin, Trachine | [7] |
| Gurnard perches (Neosebastidae) | Anterolateral glandular groove in venomous dorsal or anal fins spine | Myotoxins | [7] |
| Scarpionfish (Scorpaenidae) | Anterolateral glandular groove in venomous dorsal or anal fins spine | Sp-CTx, Sp-GP, SNTX | [7] |
| Waspfish (Tetrarogidae) | Anterolateral glandular groove in venomous dorsal or anal fins spine | VTX, TTX | [7] |
| Stonefish (Synanceiidae) | Anterolateral glandular groove in venomous dorsal or anal fins spine | VTX, | [7] |

**Table 4: Major fish toxin and their mode of action**

| S. No. | Toxin | Mode of action | Source |
|---|---|---|---|
| 1. | Verrucotoxin (VTX) | Exert negative inotropic and chronotropic effects via the inhibition of Ca channels and the opening of K channels. VTX acts as a β1-adrenoceptor agonist via the cAMP-PKA pathway, which then leads to an increase in L-type Ca2+currents. | [27] |
| 2. | Stonustoxin (SNTX) | Hemolytic activity due to the formation of pores, approximately 3.2 nm in diameter, in erythrocyte membranes. | [39] |
| 3. | Trachynilysin (TLY) | Increase the Ca2+entering in the cell and cause the formation of cationic pores in cell membranes through irreversible membrane insertion. | [42] |
| 4. | Sp-CTx | Biphasic vasoactivity and hemolytic activity by pore formation in cell membranes and forms molecular aggregates. | [44] |
| 5. | Karatoxin | Cytolytic, Mitogenic, and Chemotactic effects | [46] |
| 6. | Cardioleputin | Displays inotropic and chronotropic | [50] |
| 7. | Dracotoxin | Caused hemolysis via membrane depolarization from interactions with membrane glycophorin. | [54] |
| 8. | SA-HT | Hemorrahagic activity to cutaneous tissue also produced edema, capillary permeability, muscle contraction or relaxation, mast cell degranulation | .[55] |
| 9. | TmC4-47.2 | Causing depolarization on frog neuromuscular junctions. | [58] |
| 10. | Nattectin | Induces M1 macrophage marker iNOS, and up-regulate the expression of MHC class II, CD80, CD86 and CD40 molecules, | [60] |
| 11. | Wap | Have pro-inflammatory action, by increasing the number of leukocytes rolling and adhering to the endothelium. | [61] |
| 12. | Toxin-PC | Have non-competitive neuromuscular blocking activity in cardiac tissues via interactions with K+channels. | [62] |
| 13. | Toxin I and Toxin II | Edema-forming and nociceptive activities. | [63] |
| 14. | Pardaxin | Antibacterial activity via pore-forming in cell membranes | [66] |
| 15. | Orpotrin | Elicit vasoconstrictive effects on mouse cremaster muscle. | [69] |
| 16. | Porflan | Shown to be pro-inflammatory by increasing rolling leukocyte numbers in mouse cremaster muscle post-capillary venules. | [71] |
| 17. | Grammistrins | Antibacterial activity via membrane-lytic. | [76] |
| 18. | Kallikrein | Edematic activity. | [83] |

**Table 5: Toxicity type of fish venom toxins**

| Name of fish toxin | Cytotoxic | Neuromuscular toxic | Hemotoxic |
|---|---|---|---|
| SNTX | +C | +N | +H |
| SP-CTx | +C | - | +H |
| VTX | - | +N | +H |
| TLY | +C | +N | - |
| NeoVTX | - | - | +H |
| Gramistins | +C | - | - |
| Crustins | +C | - | - |
| Kallikrein | - | - | +H |
| SA-HT | - | +N | +H |
| Paradoxin | +C | - | - |
| Epinecidin | +C | - | - |
| Plumieribetin | +C | - | - |
| SP-CL-5 | +C | - | - |
| Dracotoxin | +C | - | +H |
| Cardioleputin | +C | +N | - |
| WAP domain | - | - | +H |
| Orpotrin | - | +N | +H |
| TmC4.47.2 | - | +N | +H |
| TTX | +C | | - |
| Dracotoxin | - | - | +H |

*+C indicates cytotoxic,+N neurotoxic,+H hemotoxic, the negative sign shows no activity

**Table 6: Some fish toxins and their pharmacological activity**

| Fish toxin | Mode of action | Pharmaceuticals uses | Source |
|---|---|---|---|
| SNTX, Sp-CTx, Trachynilysin | Pore formation in cell membrane | Cytotoxic use as antipathogenic | [43, 45] |
| TnP | Damage tissue repairing | Use in multiple sclerosis | [55] |
| Karatoxin | D-manose binding lectins | Cytotoxic,Mitogenic,Chemotactic | [48] |
| Gramistins | membrane-lytic activity | Antipathogenic, antibacterial | [77] |
| Tetrodotoxin (TTX) SA-HT | Axonal conduction blocker Mucscle contraction and relexation | Analgesics | [162] |
| Crustins I, Crustins II | cells lysis by protease activity | Antimicrobial | [124] |
| Pardoxin, Epinecidin | pore-forming polypeptide and iduce apoptosis | Anticancerous, Antibiotic, Antimicrobial | [102] |
| WAP-domains peptides | Pro inflamatiory increases no of leucocytes | Wound repair,tissue regeneration or stimulate ecdysis | [125] |
| Arabian gulf catfish | Tissue repair | Stimulate rate if wound healing | [163] |
| Nacitoxins | Ca++channel blockers | Analgesics | [164] |

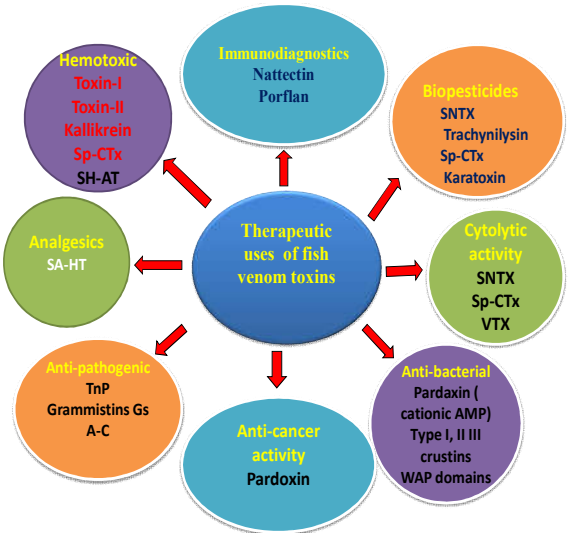
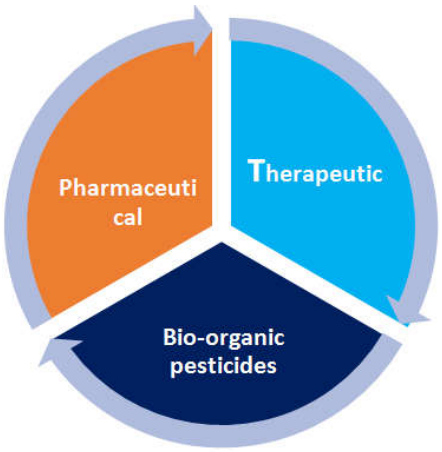
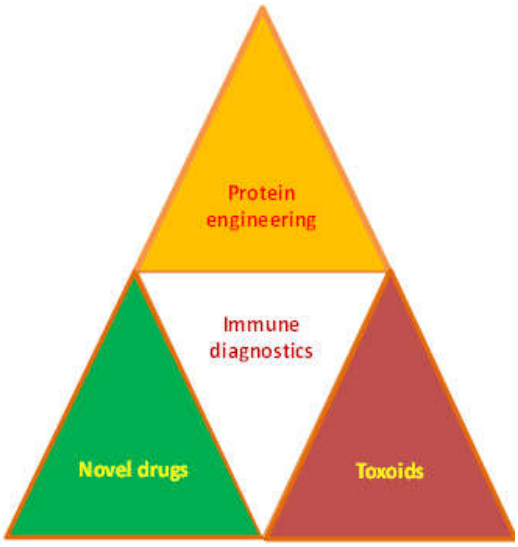



**Fig. 1: Various biological activities of fish venom toxins**




**(a)**




**(b)**

**Fig. 2a, b: Pharmaceutical, therapeutic and biopesticidal uses of fish venom toxins**

**Karatoxin**

Karatoxin was isolated from dorsal spines of the Redfin velvetfish *H. rubripinnis* venom. This is a 110 kDa complex that acts as a D-mannose binding lectin [46]. It shows cytolytic, mitogenic, and chemotactic effects, as well as agglutinating effects on rabbit erythrocytes [47, 48] (table 4).

**Cardioleputin**

Envenomation by *S. plumieri* is quite hazardous, provoking extreme pain and life-threatening [49]. Fish inflicts cardioleputin a 46 kDa protein that displays inotropic and chronotropic effects on guinea pig atria [50]. It has no cysteine residues in its structure (table 4).

**Plumieribetin**

Plumieribetin, a fish lectin homologous to mannose-binding B-type lectins, inhibits the collagen-binding α1β1 integrin [51] (table 4).

**Dracotoxin**

Dracotoxin is a 105 kDa protein isolated from weever fish, *T. Draco*. It does not cause hemolytic activity against other animal erythrocytes [52]. Dracotoxin caused hemolysis via membrane depolarization from interactions with membrane glycophorin (tables 4 and 5).

**Trachinine**

Trachine is isolated from the lesser weever-fish *T. vipera* [53]. It is composed of four identical subunits of 81 kDa each. It shows high lethality and its 2–2.5 μg doses can kill 20 g male mice instantly at *vivo* [54] (table 4).

**SA-HT**

SA-HT is an 18 kDa protein isolated from *S. argus* venom. It shows severe hemorrhagic activity to stomach walls, but lacks hemorrhagic activity [55] (fig. 1). SA-HT generates dose-dependent edema, capillary permeability, muscle contraction or relaxation, mast cell degranulation, and increased levels of placement and malonaldehyde in various animal models (table 4).

**Lectins**

A 14 kDa B-type lectin Plumieribetin was isolated venom of *S. plumieri* that inhibit α1β1 integration. A group of five isolectins (SP-1 to 5) was found in an agglutinating fraction of *S. plumieri* venom [56, 57] (table 4).

**TmC4-47.2**

TmC4-47.2 is a 15 kDa myotoxic polypeptide isolated from *T. maculosa* venom. It selectively works on skeletal muscles and increases miniature endplate potentials and causing depolarization on frog neuromuscular junctions [58] (table 4).

**Nattectin**

Nattectin is a 15 kDa toxin (C-type lectin) isolated from the venom of *T. nattereri*. It is closely related to *T. maculosa*. The intestine is a galactose-specific location that causes agglutination of human red blood cells. It induces neutrophil mobilization in mice in a Ca2+independent manner [59]. Nattectin enhances integrin-mediated cell adhesion in HeLa cells and improves their resistance to apoptosis [60]. It shows a potent pro-inflammatory capacity. Nattectin induces M1 macrophage marker iNOS, and up-regulate the expression of major histocompatibility complex (MHC class II), cellular differentiation (CD80, CD86, and CD40 molecules) [60] (table 4) (fig. 1).

**Wap**

WAP (whey acidic protein) are proteins having a WAP four-disulfide core (WFDC). These are not only found *C. spixii.* in fish but also present in mammals (including marsupials and monotremes) birds, reptiles, and amphibians. Most of them show protein inhibition, and inhibit calcium transport). A 65-kDa Wap family protein (Wap65) is isolated from sting venom of It shows pro-inflammatory action, by increasing the number of leukocytes rolling and adhering to the endothelium. [61] (table 4) (fig. 1).

**Toxin-PC**

Toxin-PC found in Indian catfish *Plotosus canius.* It shows LD50 225 micrograms/kg when given intravenously in mice. It also shows the cytotoxic activity as a neuromuscular blocking activity. Toxin-PC generates cardiac arrest on the isolated toad and guinea pig hearts. These proteins develop Ca++ion-dependent tension in contractile muscle cells. Neuromuscular blocking time lowers down as the *K+*ion concentration was increased in the medium. It shows non-competitive neuromuscular blocking activity in cardiac tissues via interactions with K+ channels [62] (table 4).

**Toxin I and Toxin II**

Toxins I and II are monomeric simple proteins with almost the same molecular mass (35 kDa for toxin I and 37 kDa for toxin II). Both are isolated from oriental catfish *Plotosus lineatus* and display lethal, edema-forming and, nociceptive activities (fig. 1). Toxins I contain 317 amino acid residues while II 315 amino acid residues share as high as 86% sequence identity with each other. This is also highly homologous (56-75% identities) with the known fish natterin-like proteins [63] (table 4).

**Pardaxin**

Pardaxin (PX) is a 33-amino-acid pore-forming polypeptide toxin isolated from the Red Sea Flatfish *Pardachirus marmoratus*, has a helix-hinge-helix structure. It selectively works on bacterial membranes (e. g., scraping), display cytotoxic activity like melting and kill mammalian erythrocytes. It shows much similar potency with magainin, cecropins, and dermaseptins anti-bacterial peptides (table 1). Furthermore, a positive charge added to its N-terminus significantly increased its antibacterial against gram-positive bacteria, but this charge abolished its low hemolytic activity [64]. Its secondary-structure laminated analogs show 25-80% more alpha-helical content in 40% CF3CH2OH/water than their non-animated form [65]. Pardaxin produces postjunctional muscle contraction in guinea-pig intestinal smooth muscle could be used for drug development [66] (table 4) (fig. 1 and 2).

**Bioactive peptides**

Bioactive peptide isolated from fish venom showed harmful effects, such as venular stasis, hemorrhage, and changes in the arteriolar wall diameter. These generate a typical inflammatory activity in post-capillary venules [67] and increased the frequency of the spontaneous release of acetylcholine at the neuromuscular junction by up to 100-fold [68] (table 4).

**Orpotrin**

Orpotrin is a 49-day peptide having linear HGGYKPTDK amino acids in the main chain [69]. This is isolated from *Potamotrygon grorbignyi* freshwater stingray venom. It elicits vasoconstrictive effects on mouse cremester muscle when applied topically [69] (table 4 and 5).

**Porflan**

Porflan is a bioactive peptide isolated from *P. orbignyi* with a mol wt of 2.0 kDa. It shows no homology to any known peptides and proteins [70]. It shows pro-inflammatory effects by increasing rolling leukocyte numbers in the mouse cremaster muscle post-capillary venules [71]. Porflan does not cross biological membranes unassisted and therefore may target active transport and extracellular domains to elicit activity [72] (table 4).

**Grammistrins**

Grammistins toxin peptides found in Soap fish *Grammistes sexlineatus* and *Pogonoperca punctata*, in skin secretions. *Grammistes sexlineatus* contains two grammistins (Gs 1 and Gs 2) while *Pogonoperca punctata,* six grammistins (Pp 1, Pp 2a, Pp 2b, Pp 3, Pp 4a and Pp 4b) [73-75]. Grammistins (Gs A-C) exhibit broad-spectrum antibacterial activity, but do not show hemolytic activity. Grammistins (Gs A-C) exhibit broad-spectrum antibacterial activity but do not show hemolytic activity (fig. 1). Grammistins Gs A-E, Gs 1, and Gs 2 could release carboxyfluorescein entrapped within liposomes made of either phosphatidylcholine or phosphatidylglycerol/phosphatidylcholine (3:1) and display membrane-lytic activity in cells [76-79] (table 4).

**Kallikrein**

*T. nattereri* venom possesses a tissue-kallikrein-like enzyme that causes inflammation and plays a role in nociception and edema. The toxic components of *T. nattereri* venom contain the 5 proteins called Natterins which make a novel toxin family [80, 81]. The Natterins range in size from 41.4 kDa (Natterin 4, 387 amino acids) to 5.9 kDa (Natterin P, 71 amino acids). These show kallikrein activity and are allodynic and edema inducing [82] (table 4). Natterins cleave type I and type IV collagen fibers and impose necrosis in affected cells [83-85]. Natterins inhibit interactions between leukocytes and the endothelium, and reduce neutrophil accumulation and show lighter anti-inflammatory effects [86]. These effects depend on negative signals generated from the TLR2-TLR4/Myd88 signaling cascade that is mediated by the activation of serine/threonine phosphatases and key signaling of the PI3K molecule [87]. Fish crude venom upon sudden infliction causes hemolytic, cardiovascular, neuronal skeletomuscular dermonecrotic, edema-promoting, vasospastic, erythema, swelling, severe pain, or cyanosis and necrosis in tissues (table 4) (fig. 1).

Toxicity found in fish toxins is species-specific and each one of them displays major biological activity. These either act or inhibit specific ion channels in muscle cells and nerve cells and impose neuromuscular activity. Stonustoxin (SNTX) shows hemolytic activity due to the formation of pores, approximately 3.2 nm in diameter, in erythrocyte membranes while gramistins, paradoxin, epinecidin, SP-CL-5, dracotoxin, and cardioleputin show cytotoxic activity (table 5).

**Enzymes**

**Hyaluronidases**

Hyaluronidase enzymes have been isolated from *S. horrid*, *P. motora,* and *S. verrucosa* venoms [88]. These enzymes possess an approximately a molecular weight of 62-79kDa and contain three N-glycosylation sites [89]. All these enzymes are closely related but showed less than 50% identity [90, 91]. These relatively showed a high affinity to the hyaluronan substrate [92]. Hyaluronidases isolated from lionfishes *P. volitions* and *P. antenatal* showed 99.6% sequence homology to each other and 72%–77% homology with the stonefish hyaluronidases. The lionfish hyaluronidase sequences show five possible glycosylation sites, and three of them are found in both stonefish hyaluronidases [93].

**Non-proteinaceous components**

Fish venom also non-proteinaceous active compounds *T. vipera* venom contains 5 hydroxytryptamines (5-HT), commonly known as serotonin, which is a well-known nociceptive compound [94, 95]. *G. marmoratus* venom also contains 5-HT, or a 5-HT-like substance acts directly at 5-HT receptors and whose action was attenuated by a 5-HT receptor antagonist. Stonefish venoms contain norepinephrine, but do not possess serotonin [96]. *S. verrucosa* venom was found to have relatively more norepinephrine when compared to *S. horrida*, but relatively less dopamine and tryptophan [97]. These compounds impose cardiovascular effects like SNTX and VTX toxins. A small non-proteinaceous toxin, with a molecular weight of 3.27 kDa, was isolated from the *P. volitions* venom and found to induce paralysis in victims. [98] *P. volitions* venom also contains acetylcholine, and its role is still unexplored [99].

**Mode of action**

Fish toxins are charge bearing molecules that bind to selected ion channels, pumps, transporters, and ligand-gated ionotropic receptors and exerts their effects on intracellular ion homeostasis. Fish toxin components also act through G-protein-coupled and tyrosine kinase receptors and impose discrete effects, alter second messengers towards pathological levels. Toxins after their movement and arrive in tissues and enter inside cells through specific ports and target metabolic functions of subcellular organelles such as mitochondria, nucleus, protein-and RNA-synthesis machinery and cytoskeletal networks. These also targets exocytic vesicles and deregulated their normal activity.

Because of diverse structural amino acids, different toxins interact at different specific sites of action. They modulate or accelerate the activity/intensity of their binding and cell type interests. They differently interact with secondary messengers and signaling cascades in the host after their infliction. While the interaction target site is largely determined by the chemical nature of the toxin. Once, after finding a way inside the cell, toxins affect several ubiquitous secondry messengers and protein kinases/phosphatase pathways and impair them (table 4).

**Biological activity of fish venom**

The lethal toxin of *S. trachynis* venom (TLY) releases acetylcholine from the neuromuscular junction. Some of the toxins have neurotoxic effects which include paralysis of hind limbs, muscular weakness and higher doses causes coma and respiratory failure. Tetrodotoxin (TTX) a toxin peptide blocks axonal conduction action in victims and its activity depends on the extracellular Ca2+level. It also blocks serotonin or histamine H1 receptors, tachykinin NK1 receptors, and do functional impairment of capsaicin-sensitive sensory nerve endings or inhibition of cyclooxygenases contractile activity. *Scatophagus argus* (Scatophagidae) venom contains phosphodiesterase, acid phosphatases, alkaline phosphatases, proteins, and caseinolytic activity. The venom induces painful wounds, local tissue damage with severe pain, edema, inflammation and, necrosis in a fisherman. It also causes acute muscle damage in the gastrocnemius muscle of experimental mice (table 6).

Many of the fish venoms contain toxin responsible for erythrocyte lysis. The mechanism behind erythrocyte lysis is the formation of hydrophilic pores in the cell membrane. SNTX, trachynilysin, and Sp-CTx form pore in cell membranes. Karatoxin exerts cytolytic, mitogenic, and chemotactic effects, and do agglutination of rabbit erythrocytes [100]. Enzyme PLA2 (phospholipase 2) also causes hemolysis. Stonustoxin causes endothelium-dependent relaxation at low concentration while *P. volitions* venom induces a hypotensive response whereas *S. trachynis* venom produces a hypertensive response (table 6).

Fish venoms show multiple effects and display toxic and physiological changes in the vertebrate system. The venoms target a variety of physiological systems and processes to deter potential predators. It acts in three ways it binds to receptors by ligand-gated channels, affects ion channel, and shows direct permeability functions. The most potent effects of poison venoms are on the cardiovascular system. All piscine venoms produce profound cardiovascular changes, both *in vitro* and *in vivo*, including the release of nitric oxide from endothelial cells. It increases smooth muscle contraction, and squeeze atria. In addition to their cardiovascular effects, piscine venoms possess neuromuscular activity. Among general effects are headache, vomiting, abdominal pain, hypertension, hypotension, cardiac arrhythmias and arrest, convulsions, collapse, shock. The Most important physiological effects seen are severe pain, swelling, sweating, and blistering, bleeding, necrosis. These toxins also cause specific systemic effects like paralytic and hemorrhagic. These cause neurotoxicity, neuroexcitatory neurotoxicity, myotoxicity, interference with coagulation, renal toxicity, cardiac toxicity venom induces an acute inflammatory response (fig. 1).

Fish venoms are comprised of a large number of components such as enzymes, small peptides, and proteins, non-proteinaceous molecules with diverse biological activities (table 5).

**Cytolytic activity**

Scorpaenoid toxins, SNTX, trachynilysin, and Sp-CTx, form pores in cell membranes and exhibit catalytic activity. Karatoxin also showed cytolytic, mitogenic, and chemotactic effects, as well as agglutinating effects on rabbit erythrocytes [101] (fig. 1). Pardaxin is a cationic antimicrobial peptide derived from Red Sea Flatfish that causes cell death. The cell death mechanism involves endoplasmic reticulum (ER) targeting and c-FOS induction. Treatment with pardaxin also increased the level of calcium, and blockage of cellular calcium signaling is disrupted pardaxin-induced cell death [102] (table 6).

**Hemolytic activity**

Fish venoms cause hemolytic that depends on the species, toxin type, action, and sensitivity [103]. These cause severe pain in the limbs,

mainly swelling in regional lymph [104-105] that results in edema and erythema [106, 107] (Tables 2 and 3). *T. Draco* crude venom, dracotoxin showed cause hemolysis of erythrocytes, with an EC50 of 3 ng/ml in rabbit [108, 109]. Fish venoms also possess the ability to lyse with other cell types. *S. Argus* venom has been found to cause the loss of HeLa cells and platelets [110] (fig. 1). The venoms of the toadfish, *Thalassophryne nattereri*, and *S. horrida* both possess platelet-lysing activities as well, but *S. horrida* venom does not cause significant losses of HeLa cells [111, 112]. *Hypodytes rubripinnis* also causes strong hemolysis in rabbit erythrocytes, but *P. lunulata* showed a 10 fold higher activity than *I. japonica* and 100 fold higher activity than *H. rubripinnis.* In a few animal venoms, phospholipase A2 (PLA2) causes cytotoxic activity. [113], but most of the piscine venom lack PLA2 proteins [114-116]. Instead, hemolysis fish venoms use act through alternative mechanisms. Oriental catfish, *Plotosus lineatus*, secretes at least one hemolysin, two lethal factors, and two edema-forming factors. These venoms secreting glandular cells are found near the dorsal and pectoral stings in the fish epidermis (table 6).

**Proteolytic activity**

Fish venom contains enzymes which show different peptidase activities [112]. *S. Argus* venom has both alkaline and acid phosphatase activity, as well as phosphodiesterase activity [112] (fig. 1). Marine stingray *D. guttata* and the fluvial stingray *P. falkneri*, contain proteolytic enzymes against casein, gelatin, and fibrinogen. The similar proteolytic activity is also found in *P. scobina* and *P. orbygnyi* crude venoms against casein [113]. Proteolytic enzymes are stable and act much similar to zymogen [113]. Both *G. marmoratus* and S. *Horrida* possess these enzymes, as well as exteriors [113]. Additionally, angiotensin-converting enzyme activity was found in *T. nattereri* venom, where it contributes to the venom's inflammatory response [114] (table 6). Proteolytic activity was also found with the toadfish *T. nattereri* and *T. maculosa* and the catfish *A. thallasinus*, and the butterfish *S. argus* [114, 115]. *T. nattereri* venom was shown to have gelatinolytic activity. Fishes *P. heinlein*, *N. robust*, and *P. volitans* contain proteases (45-97 kDa Mol wt). The venom of *S. Plumier* was found to have proteolytic activity against both casein and gelatin. Fish venoms contain several enzymes other than proteases.

**Neurotoxic activity**

Fishvenoms from six species, mainly cartilaginous stingrays *Neotrygon kuhlii* and *Himantura toshi,* and the bony fish *Platycephalus fuscus*, *Girella tricuspidata*, *Mugil cephalus*, and *Dentex tumifrons* show neurotoxic effects in experimental animals (10-100 µg/kg). *P. Fucus* venom exhibits a hypotensive response, while venom from *G. tricuspidata* displayed a single depressor response. *N. kali*, *H. Toshi*, and *P. fucus* venoms caused concentration-dependent inhibition of indirect twitches in the chick biventer cervicis nerve-muscle (CBCNM) preparation [116]. These three venoms also inhibit responses to exogenous acetylcholine (ACh) and carbachol (CCh), but did not obstruct potassium chloride channel (KCl), and saw a post-synaptic mode of action (fig. 1). Venom from *G. tricuspidata, M. cupolas,* and *D. tumifrons* had no significant effect on indirect twitch organismic responses in the chick biventer cervicis nerve-muscle (CBCNM) preparation [117] (table 6).

**Cardiovascular activity**

Most of the fish venom toxins induce cardiovascular collapse at a very low dose i.e. 200 µg/kg when provided intravenous treatment in animals. Indian catfish *P.* canis *Hamilton* (locally called 'Kan major') venom generates a positive inotropic effect on toad and rabbit hearts at a low dose, while at higher doses it produces cardiac arrests and affects pharmacodynamic activity. Its LD50 was determined at 3.9 mg/kg (IP). Catfish *C. spixii* venom induces rolling and adherent leukocytes in the post-capillary venules of the Cremaster muscle of mice. It increases vascular permeability in the peritoneal cavity. Catfish venom induces contractions in several smooth muscle preparations viz., ileum and colon of guinea pig, fondues, uterus, and ileum of the rat. On isolated guinea pig ileum, catfish venom produced contraction which was not antagonized by atropine and mepyramine but was partially antagonized by methysergide [118].

The crude venom of *P. maculatus stinger* induces marked nociceptive and edematogenic effects and affects vascular permeability at doses from 30 to 100 µg/animal. Though, it did not cause hemorrhage and no effect on clotting times but show significant changes in the levels of CK and its isoenzyme CK-MB in mice (tables 4 and 5) [119]. The Arabian Gulf catfish (*Arius thalassinus,* Ruppell) produces toxic substances from its skin show cholinergic vasoconstrictor activity in umbilical and renal arteries of sheep (table 2). [120].

**Inflammatory activity**

*P. fasciatum* venom induces an acute inflammatory response characterized by the recruitment of immune cells into peripheral tissues choreographed by chemoattractants including lipid mediators (LTB4 and PGE2), cytokines (IL-1β and TNF-α), and chemokines (KC and MCP-1). It causes acute inflammation as pain in which serotonin, leukotriene, and prostaglandin are involved in edematogenic and nociceptive responses (fig. 1). Since a selective COX-2 inhibitor, a non-specific inhibitor for cytokines and COX-2, and a non-selective 5-HT receptor antagonist were able to reduce both symptoms [121] (table 6).

Mucus induced the recruitment of neutrophils immediately after injection followed later by macrophage infiltration. Sting venom-elicited peritoneal macrophages lost the ability to differentiate into dendritic cells. It is caused due to cellular infiltration of toxins. Toxins also provoke peritonitis reaction characterized by cytokine (IL-6), chemokines (MCP-1 and KC), or lipid mediator (LTB4) production in the peritoneal cavity. Sting venom does not express CD11c, nor do they exhibit sufficient levels of MHC class II. Fish toxins; promote inflammatory reaction that is induced by antigen persistence in the peritoneal cavity and activation of phagocyte cells [122, 123].

**Anti-cancerous activity**

Pardaxin selectively triggers the death of cancer cells when used *in vitro* cell culture. Its action starts with an increase in c-FOS expression that induces cell death in diverse cancer cell lines. Immunofluorescence staining of cleaved caspase-3 in SCC-4 cells revealed that the expression of activated caspase-3 in SCC-4 cells significantly increased after 24-h treatment with pardaxin. Pardaxin treatment also causes cell cycle arrest of SCC-4 cells in the G2/M phase, thereby limiting cell proliferation. Pardaxin induces apoptosis, activated caspase-7 and interleukin (IL*)*-7r, and down-regulated caspase-9, ATF 3, SOCS3, STAT3, cathelicidin, p65, and interferon (IFN*)*-γ. It induces apoptosis through the death receptor/nuclear factor (NF*)*-κB signaling pathway after 14 d of treatment in tumor-bearing mice. Production can be used as a potential marine drug that can finish fibrosarcomas and oral cancer (fig. 1). *P. volitans* venom selectively induces apoptosis in HEp2 and HeLa cells *in vitro*. It shows strong anticancer potential against cancer cells and does not show any deleterious effects on human lymphocytes (table 6).

**Antimicrobial activity**

Fish toxins contain antimicrobial peptides (AMPs) that act on the membrane of microbial cells and cause cell lysis. Pardaxinis a cationic AMP that shows antimicrobial potential to be used as a novel antibiotic. *S. marmoratus* six AMPs i.e. Hepcidin 1, liver-expressed antimicrobial peptide 2 *(*LEAP-2), Piscidin, Moronecidin, NK-*lysine,* and β-*defense*. These are used to kill pathogen infection in aquaculture [124] (tables 2 and 3). Most of Type I and II Christians are antimicrobial towards Gram-positive bacteria, whereas the Type III Christians tend to display protease inhibition. Fish venom contains WAP domains that are found conserved in so many species of fish and operate in diverse physiological processes such as protease inhibition, bacterial killing, or inhibition of calcium transport [125]. Epinecidin shows higher antibacterial potential than synergistic streptomycin and kanamycin against methicillin-resistant *Staphylococcus aureus.* AMPs are similar to broad-spectrum antibiotic drugs and show better antimicrobial activity than non-peptide antibiotics [126] (table 6) (fig. 1).

**Enzyme inhibitory activity**

Venom toxins isolated from different fish venoms such as stonefish, soldierfish, lionfish, weeverfish, and stingrays inhibit the activity of

various physiological enzymes such as proteases [127, 128] hyaluronidase and phospholipase C activity [129, 130]. These also impose various biochemical and pathological changes [131-134] which need serum neutralization of its toxic activities [135, 136]. Fish toxins also showed angiotensin processing activities [137]. *N. robusta* venom also contains hyaluronidase activity while *S. argus* possesses phospholipase C activity and causes hemolysis much similar to PLA2 found in some terrestrial venoms [138, 139]. Catfish venom contains very high hyaluronidase and lipase activity, but lesser activities of phospholipase A2, lactate dehydrogenase (LDH), cholinesterase (CE), alkaline phosphatase (ALP), and aspartate transaminase (AST), and last activity of proteins and 5-nucleotides (5'-NT) [139] (fig. 1 and table 6).

**Immunomodulatory activity**

Fish venom toxins modulate the kinetics of leukocyte influx in mouse injured footpaths, which impaired the transit of neutrophils and affect macrophage survival. It consequently results in a deficient healing phase [140]. Fish venom causes a severe local inflammatory response by aggravating macrophages [140, 142]. Both IL-4 and IFN-γ regulate M1 macrophage polarization [143]. Nattectin also affects typical dendritic cell functions but also drives T-cell responses to the Th1 phenotype [144] (fig. 1). These generate immune responses in experimental animals after administration and are used for the generation of vaccine-induced TH17 cells and IL-17 production [144]. *T. nattereri* venom strongly implies the production of IL-17A derived from effector memory T-cells [145]. *Thalassophryne nattereri* fish venom induces IL-5 production and impairs B220+cells [146]. For neutralization of natterins, protease is used that generates long-lasting innate-like B cells and plasma cells in spleen [147]. These induce differentiation of germinal center derived-memory-B cells, which transform into plasma B cells [148]. Both IL-5 and IL-17A generate chronic IgE response and differentiation of long-lived antibody-secreting cells in inflamed tissues [149]. Furthermore, the process of differentiation of long-lived antibody-secreting cells depends on integrated signals derived from antigen and IL-17A that maintain their longevity [150].

**Use of venom toxins for drug development**

From various researches, it is much clear that fish toxins contain many low molecular weight toxin peptides, enzyme, and non-proteinaceous components. These components interact with various biomolecules, bind to various receptors, and exert physiological and biological effects through intracellular signaling via discrete portals [151, 152]. Fish venom peptides and proteins are pharmacologically active components that could be used for drug development [153, 154] (tables 4 and 6) (fig. 2a and 2b). To date, so many animal venom components have been transformed into drugs for therapeutic uses [155]. Researchers are using toxibioinformatic data of various animal toxins to make new much potent pharmaceutics and diagnostics (fig. 1a, 1b, 1c) [156, 157]. These drugs are fast-acting, highly specific, and target receptor and ion channels and relieve pain [158, 159]. These drugs work in various capacities as neuronal inhibitors, analgesics, and neuromodulators and proved clinically effective [160]. Besides, there are few demerits of these toxin-based drugs as they often lose their potency and accuracy when used as a medicine in the human body.

There is a possibility that these drugs may hit some alternative targets and non-selective due to low potency range. After its use unexpected side effects cannot be denied (tables 4 and 6). Because of their larger size, these could not pass through the blood-brain barrier in comparison to small synthetic molecules; by contrast, they pass this barrier more easily. These venom based drugs are mainly peptides and proteins cannot be taken orally if swallowed may have deadly consequences [161]. The real fact is that during drug development bio-informatics parameters of natural toxins change (venomics) that may generate adverse physiological effects [162]. It also affects receptor binding and signaling pathways which activate the innate immune response in the patient [163]. This is the main reason that natural venom interacts with physiologically important molecular targets and affects the vital function of organisms in a different manner rather than a toxin template [164, 165]. Toxin based drugs that relieve pain are widely-used in preparation of analgesics [166] and other therapeutic purposes [167] (fig. 2a and 2b).

Venom toxin structures are also important and there is a need to make interconnection among biochemistry, pharmacology, and immunology areas for the expansion of knowledge and the generation of innovation. By using their bio-informatics data [168] fish toxins peptides can be used to generate novel drugs [169], immune diagnostics, toxoids, and pharmaceuticals, for therapeutic purposes [170, 171] (fig. 2a and 2b). Toxin templates can be used for the generation of new novel less toxic target specific therapeutic drugs by making slight modifications in their structure. Fish venom has much wider biomedical applications and can be used for the production of bio-pesticides, for controlling various pests of field crops (fig. 2a and 2b).

**Anti-venom therapy**

Fish envenomation represents a great cost in terms of public health, leisure, and tourism. Victims rapidly develop symptoms like pain, local swelling, erythema followed by intense necrosis that persist for long days. Marine stingrays, sharks, and catfish stings are highly fatal to the divers, tourists, and fishermen. Though first aid methods are recommended for treatment of fish toxicity, but for quick neutralization of stings fish-specific anti-venoms are provided. Medical treatment includes both general and specific measures, but anti-venom is considered to be a better tool to neutralize the effect of toxins [172]. Anti-venom is available only for a limited range of species, not for all dangerous species. There is a very short supply of anti-venoms against marine sharks and other dreadful fish stinging by giant sharks. Both synthesized antibodies and antigen-specific antibodies of high affinity which show specific immune response efficiently minimize the symptoms of intense and immediate inflammatory reactions caused by fish venom. Anti-venom therapy successfully neutralizes the deleterious effects [172] caused by fish venom toxins and provides life protection cover to victims [173]. But unfortunately, supplies of life-saving anti-venoms are scarce, and this scarcity particularly affects rural populations [173].

**CONCLUSION**

Fish toxins are highly specific as they show diversity in the structure and function belongs to different families. Fish venom is a good source of proteinaceous toxins and enzymes mainly smaller protein toxins, and non-proteinaceous molecules. These components are highly active toxic agents as they generate multiple clinical and pathophysiological symptoms. Fish toxins showed various biological activities such as humorless, cause severe pain upon envenomation. Besides, fish toxin biological information can be exploited to generate new knowledge about the evolutionary relationships between venomous animals and their prey. For quick neutralization of fish toxicity, antigen-specific antibodies of high affinity are synthesized these could minimize the symptoms and immediate inflammatory reaction caused by fish venom.

**ABBREVIATIONS**

ACh-Acetylcholine, ALP-Alkaline phosphatase, AMPs–antimicrobial peptides, AST-Aspartate transaminase, CE-Cholinesterase, 5-HT-Hydroxytryptamine, LDH-lactic dehydrogenase, NK-natural killer cells, PX–Pardaxin, SNTX-Stonustoxin, TLR-Toll-like receptors, TLY-Trachynilysin (TLY), VTX-Verrucotoxin, Whey acidic protein-WAP

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The authors declare no competing financial interests.

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