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Pharmacological studies of oil sardine fishes

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***Abstract*---**The current review article discusses the toxins of different species of fish as well as their pharmacological and therapeutic applications. Fishing in coastal areas is a major concern because it can cause serious poisoning to fishermen, residents and visitors. Toxins from fish can cause severe discomfort, which can spread to the extremities and the lymphatic system. It may also result in venous stasis, hemorrhage, and alterations in the diameter of the artery wall. Particle channels, ligand-gated channels, and G-protein-coupled receptors in body cells are totally impacted by fish poisons as far as physiological and metabolic exercises. They damage the signaling molecules, causing hemolysis, cardiovascular problems, impaired nerve activity and smooth muscle contraction. The effects of fish venom on specific antibodies to the toxin are used for rapid neutralization. It reduces pain, reduces symptoms and stops the inflammatory process in its tracks. Fish poisons have a wide range of medicinal uses and their biological information can be used to develop immunological diagnoses, biocides, anticancer drugs and analgesics.

***Keywords*---**pharmaceutical activity, envenomation, anti-venom therapy, bio-pesticides, fish toxin.

Introduction

Toxic organisms may be found in a broad range of species and contain a wide range of poisons that target a wide range of targets, resulting in a wide range of clinical symptoms and mortality. Toxin-secreting cells may be located under the dorsal and thoracic spines of fish, and they swiftly create stings. Freshwater stingrays and catfish cartilage stingrays have been linked to diver healing through a mechanism that is similar to the venomous and venomous effects of marine species like Notarygan Kuhli and Himantura Toshi, brittle fish like Platycephalus

fucus and Girella trichopidata, Mugil, and Disexpha. Venomous glands may be seen in the pectoral and dorsal fins. Catfish have three perforated poisonous bone marrows in their dorsal and pectoral fins, which are fed by subepithelial glandular tissue and are employed for predator defence. Some fish, on the other hand, lack killing glands near the sting and instead cause painful wounds devoid of venom. There are around 200 toxic fish species in the globe [1-6]. Approximately 2,000 ray-finned fish are poisonous, according to current estimates based on the development of toxicology and evolution. Despite the fact that there are over 2,000 kinds of dangerous fish, fish poisons are seldom mentioned in the literature. More over half of all poisonous vertebrates are found in fish [7]. Despite their enormous biological variety, most deadly fish have comparable venom and pharmacological techniques [7-10]. Fish is an aquatic creature that may be toxic to people and cause medical issues. Fish poisoning is a severe hazard for fisherman, surfers, divers, and visitors [11-13]. Tourists who undertake sea-surfing or open-sea navigation and are at high risk of being bitten by fish are the most common victims of fish poisoning. Sharks and beams collide at random, attacking swiftly. When diving into the deep water, big carp offer a higher number of lethal threats. Humans may be injured or poisoned by stingrays and catfish in freshwater. Fish poisons have different clinical effects depending on the species and kind of toxin (Fig. 1). The most outrageous wellbeing impacts incorporate extreme restricted torment, edema, perspiring, migraine, spewing, stomach inconvenience, hypertension, hypotension, ulcers, dying, shock, loss of motion, tissue putrefaction, heart failure, spasms, breakdown, and even demise. Results (Fig. 1, Table 1). Loss of motion, hemorrhagic, neurotoxic, myotoxic, nephrotoxic, and cardiotoxic impacts have all been archived in fish harms from different species (Table 1).The assignment of immune cells to peripheral organs is governed by lipid mediators (LTB4 and PGE2), cytokines (IL-1 and TNF-), and chemokines, culminating in a severe inflammatory response (KC and MCP-1) (KC and MCP-1). [13–15] Bites from catfish may result in significant tissue necrosis and poisoning. Catfish stings cause severe inflammation, including hemolysis, cutaneous necrosis, edema, and vasospasm, as well as cardiovascular and neurotoxic effects (Table 2). The venom is injected via the dorsal and thoracic spines of marine fish, primarily catfish [15]. Fishing has a range of distinct properties in various species and is inherently advantageous for quick hunting and self-defense [16-20]. Fish bites may cause significant pain, inflammation, and lymphadenopathy when exposed to lead. Secondary bacterial infections and synovitis, for example, are frequent complications. The essential treatment for fish harming is to ease intense uneasiness by inundating the distressed area in steaming hot water (ordinarily 45-50 C) for a drawn out time allotment or until the aggravation blurs. In medical therapy, both broad and particular criteria are applied. To recover fast, patients need suitable treatment, which may involve antibody / antibody therapy. Antivirals are often ordered and prescribed by doctors. Specific antitoxins, on the other hand, seem to be a successful intervention for human immunotherapy protection. It has the capacity to prevent toxins from damaging tissues.

Data Source and Research Methodology to Identify Relevant Research

To carry out our projects, we used Medical subject headings (MeSH) and key text keywords such as "Fish Toxins and Toxins," which was added in 2019, "Organic

and Pharmacological Effects," "Method of Action," "Medication Development," and "Counteragent Therapy." As a result, a list of distributed examinations remembering data for Fish Poison Information Centers was identified. To perform a complete abstract search, these assertions are used independently and in combination. To refresh the subject and add new information, search COPUS, Web of Science, and EMBASE, as well as Pubmed, Swissprot, and Google Scholar. Choose a final measure and give a summary of the ramifications and conclusions in light of this cross-breed innovation.

Poison Composition

Fish toxins have molecular weights ranging from 50 to 800 kDa. Fish toxin comprises both protein and non-protein damages. Hyaluronidase, anguish producing factor, narrow porousness component, and species-explicit toxic elements are examples of proteins. The non-narcotic route is often accountable for the nociceptive impact of certain protein components in fish toxin. These are hazardous mixtures that have pathogenic consequences. The cardiovascular, neuromuscular, cytotoxic, hemolytic, provocative, enzymatic, nociceptive, immunomodulatory, antimicrobial, and anticancer frameworks all include substances/parts with pharmacological consequences [21, 22]. (For further details, see Tables 1 and 2.) Chimeras, beams, armed catfish, sharks, and siluroid catfish are among the venomous fish. Scorpionfish and stonefish venomous glands create vital poisons for a number of biological reasons, and their venomous glands emit significant toxins with a variety of biological actions (Table 3). (See Table 3)

The toxin of C. spixii included catfish skeletal proteins, chaperones, particle transport, glucose digestion, oxidoreductase, cell cycle, and protein binding. Fish poisons have the greatest impact on the cardiovascular and neurological systems. It has a profound impact on the atrial, causing endothelial cells to generate nitric oxide, depolarizing neuromuscular cells, and causing smooth muscle contraction. Toxins and proteins extracted from various fish species are 90% identical and have comparable effects on bodily cells and organs. Because their skeletal templates are employed in the creation of human medications and biocides (Figures 2a and 2b) [24], fish poisons are unquestionably essential in pharmacology [23].

Protein Toxins

Toxic Peptides

Stone venom, viral venom, and Sp-CTx are only a few of the primary protein poisons discovered in scorpion fish. Toxins from Synanceia verrucosa have been demonstrated to be deadly, hypotensive, and cytolytic [25]. (See Figure 1) These poisons cause the cytosol to leak out of the cell membranes, causing the cells to perish in a chain reaction. Natrinins, a toxin with kinogenic action, are found in frog venom (Table 4).

The Fungus Verrucotoxin Produces a Poison Called Verrucotoxin (VTX).

Verrucotoxin (VTX) is a poison made from the venom of S. verrucosa. It's a tetrahedron protein having a total mass of 322 kDa. Two glycosylated subunits and two glycosylated subunits (VTX) make up verrucotoxin (VTX). It has the ability to cause hypotension and heart failure in rats, as well as being lethal and hemolytic [26]. In the frog atrial myocardium, verrucotoxin (VTX) blocks Ca2 + channels while opening K channels, eliciting ionotropic and chronotropic effects [27]. This toxin also increases L-type calcium fluxes by stimulating adrenergic receptors through the cAMP-PKA pathway [28]. A second toxin, a hemolytic dimer produced of subunits, was discovered in S. verrucosa venom. A neoferocotoxin is a toxin having a molecular weight of 166 kDa (neophytex). Their viability may be harmed by ionic lipids (Table 4).

Species	Toxin	MW	Biological effects	Source
Notesthes robusta	Nocitoxin	169-174kDa	Spines are excruciatingly painful	[12]
Synanceia horrida	Trachynilysin (TLY) Stonustoxin (SNTX)	158kDa(2 subunits) 148kDa(2 subunits)	Reduce twitch height and increased basal tension, contractile response	[29]
Synanceia verrucosa	Verrutoxin (VTX) Neoverrucotoxin (NeoVTX) cardioleputin	322kDa(4 subunits) 166kDa(2 subunits) 46kDa	Cell depolarization	[28]
Scropaena plumieri	Sp-CTx Plumieribetin SP-CL1-	121kDa(2subunits) 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]

* Toxin-like toxins from rock fish (based on similarities with SNTX and VTX)

Traquinilisin is a type of traquinilisin (TLY)

Trachinilicin (TLY) is a two-dimensional protein found in the venom of S. horida. It is made up of (76 kDa) and (83 kDa) subunits. It reduces the small synaptic vessels at the motor nerve endings of the presynaptic frog. Larger, denser nucleated vessels are less effective [40]. Due to its production on endogenous acetylcholine production and its effect on mascarinic receptors, TLY reduces the rate of contraction of atrial cardiomyocytes [41]. (Table 4). This toxin enhances Ca2 + entry into the cell and stimulates chromafin cells to excrete large, densely packed nucleated vesicles. It occurs only when extracellular calcium is detected

[42]. By inserting an irreversible membrane, it causes cationic pores to form in the cell membranes [43].

Stonustoxin (SNTX)

SNTX (Stonustoxin) is a two-dimensional protein (mole with 148 codons) made up of cells [29]. A 50 This subunit and the VTX (viral toxins) [30] subunits have a high degree of sequence similarity. They're linked to neovitX and use non-covalent bonds instead of glycosylated non-disulfide bridges to bind the two SNTX (Stone Venom) subunits together [31]. There is a difference in the quantity of cysteine in these two toxins. SNTX (StoneToxin) is composed of 15 cysteine residues and 5 free thiol groups that form an intra-chain disulfide link [32]. The toxin exerts a hemolytic effect on red blood cells in mice, guinea pigs, and rabbits, but not in humans or mice [33]. The hemolytic activity of red blood cells generates holes in the membranes of mice up to 3.2 mm in diameter [34]. (See Illustration 1) This hemolytic effect produces platelet aggregation throughout the blood of the affected species. With an LD50 of 0.017g/g, SNTX caused unexpected symptoms and death in mice. Toxin residues in lysine and catechin arginine cause both hemolytic and lethal effects [35]. This toxin has a hemolytic effect but has little effect on skeletal muscle withdrawal [36, 37]. Endogenous nitric oxide (NO) or NO-delivering medicines reduce circulatory strain and endothelial-subordinate vascular unwinding significantly [38]. Synergistic vasodilation is promoted by stone toxins and endogenous hydrogen sulfide [39]. To inactivate SNTX, monoclonal antibodies produced against it are utilized. The toxin of S. verrucosa contains more norepinephrine than that of S. horida, but much less dopamine and tryptophan (Table 4).

Sp-CTx

S. plumeri was used to isolate Sp-CTx. It's a two-dimensional glycoprotein with a molecular weight of 121 kDa. [44], which possesses hemolytic and biphasic angiogenic properties, is mediated by Sp-CTx NO. (See Illustration 1) Similar to starfish venom, it produces holes in cell membranes. The toxins neoVTX, SNTX, P. volitions, and P. antenna have sequence homology with the Sp-CTx peptide. Sp-CTx forms molecular aggregates that determine the width of the poisonous hole [45]. (Refer to 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]

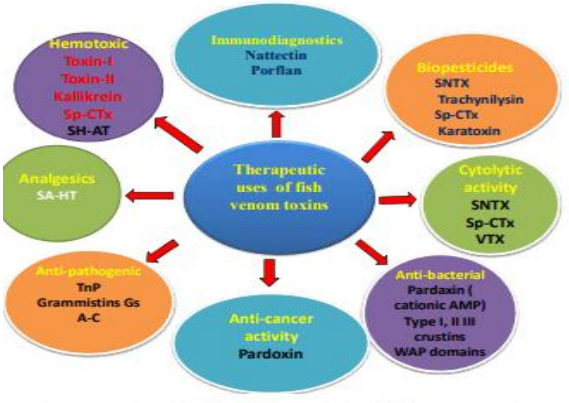

Fig. 1: Various biological activities of fish venom toxins

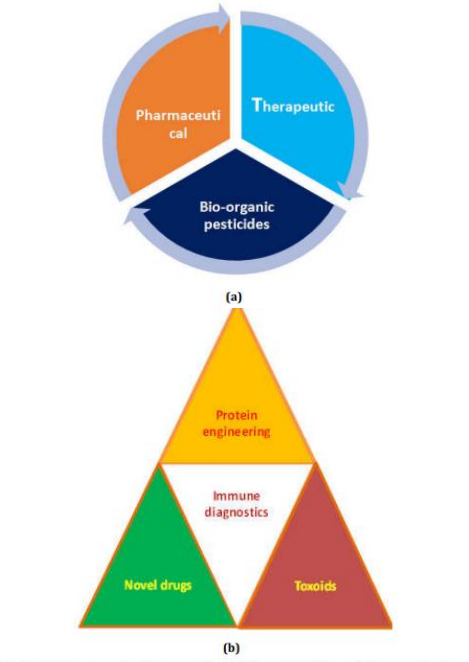

Fig. 2a, b: Pharmaceutical, therapeutic and biopesticidal uses of fish venom toxins

Cardiolibutin

Plumeric poisoning is very serious, resulting in excruciating agony and maybe death [49]. Fish produce cardiolputin, a 46 kDa protein that has einotropic and chronotropic consequences for guinea pig atria. [50]. There are no cysteine buildups in its design (Table 4).

Karatoxin

Redfin Velvet Fish h. The dorsal spine of rubripinnis was used to extract carotoxin. This compound acts as 110 kDa and Dmannose-binding lectin [46]. On red blood cells in rabbits, it has cytolysis, mitosis and chemical reactions, as well as additive effects [47, 48]. (Table 4).

Dracotoxin

T. Draco, an unidentified fish, generates dracotoxin, a 105-kDa protein. It has no hemolytic impact on erythrocytes from other animals [52]. Because of its interaction with membrane glycophorin, dracotoxin causes hemolysis by depolarizing the membrane (Tables 4 and 5).

Plumeriptine

Collagen-bound integrin 11 is inhibited by pluribetin, which binds to fish-lectin similar to B-type lectin [51]. (Table 4).

Trachinin

The trachea was isolated using T. viper, a tiny fish [53]. It is made up of four 81 kDa subunits that are identical. It's very deadly, killing 2-2.5 g doses of Vivolo 20 g male rats in seconds [54]. (See Table 4)

Nattectin

T. nattereri toxin produces Nottectin, a 15-kDa (C-type C-lectin) toxin. Maculosa's relative T. Human red blood cells concentrate in the stomach, which is a galactose-specific region. It enables neutrophils in mice to migrate without the need of Ca2 + [59]. Nectin improves apoptosis resistance in hela cells and integrated-mediated cellular binding [60]. It has potent anti-inflammatory properties. Notectin directs MHC class II articulation, cell separation, and the declaration of the M1 macrophage marker iNOS (CD80, CD86, and CD40 atoms) (Table 4) [60]. (Figure 1).

WAP (Way Acid Protein) is the protein that contains the WAP tetrasulfide center (WFDC). Hot (C). Warm blooded creatures (counting marsupials and monotremes), birds, reptiles, and creatures of land and water, as well as fish, all have them. Most of them discourage protein combination and calcium move. Wap65, a 65 kDa Wap family protein, was found in the toxin of a stinging bug. It has a favorable to provocative activity by expanding the amount of adherence to the leukocytes rolling and coating. [61] (Table 4) (Fig. 1).

SA-HT

SA-HT is a 18-kDa protein separated from the toxin of S. argus. It has extensive stomach divider dying, however no stomach divider discharge [55]. (See Figure 1) SA-HT builds edema, narrow penetrability, inotropy or unwinding, pole cell degranulation, and malonaldehyde and malonaldehyde (Table 4) levels in a scope of creature animal categories. 14 kilodaltons Lectins of Plumieribetin A Type B is a venom of S. plumeri that inhibits 11 complimentary chemicals. In the additive part of S. plumiri venom, five inlactin clusters (SP-1 to 5) were discovered [56, 57]. (See Table 4) TmC4-47.2 is a myotoxic polypeptide of 15 kDa produced from the T. maculosa toxin. It only affects skeletal muscle, increasing the capacity of the small terminal plate and depolarizing the neuromuscular connections of the frog [58]. (See Table 4)

Toxins I and II are two different kinds of toxins.

Quail I and II are monomeric proteins with similar molecular masses (35 kDa to poison 1 and 37 kDa to poison 2). (Poison 1 is 35 kDa, while poison 2 is 37 kDa). Both are obtained from the eastern catfish Plotosus linatus and have deadly, edema-forming, and nociceptive characteristics (Fig. 1). (See Figure 1). Toxins I and II 317 include normal amino acid residues, whereas Toxins III and IV 315 contain normal amino acid residues. This protein resembles well-known fish proteins such as natrin (56-75 percent identity) [63]. (Refer to Table 4)

Toxin from British Columbia

Platosus canius, an Indian catfish, contains the poison PC. It has a LD50 of 225 g/kg when given intravenously into mice. It likewise shows that its cytotoxic effect has a neuromuscular blocker impact. The BC poison actuates cardiovascular breakdown in disconnected frog and guinea pig hearts. These proteins depend on calcium particles to make pressure in contractile muscle cells. The neuromuscular barricade period diminishes as the K + particle fixation in the medium ascents. It connects with K + diverts in cardiovascular tissues to cause neuromuscular enactment [62]. (See Table 4)

Bioactive peptides are peptides that have biological activity.

Venous stasis, hemorrhage, and changes in artery wall width are caused by a biologically active peptide isolated from fish venom. These result in a 100-fold increase in the frequency of abrupt acetylcholine release at the neuromuscular junction [68] as well as typical inflammatory activity in the postcapillary veins [67]. (See Table 4)

Bordeaux

PX is a helical-joint opening framing polypeptide poison (PX) identified from the Red Sea flatfish Pardachirus marmoratus. It has cytotoxic affects, including dissolving and destroying red platelets in individuals, and operates particularly (like abrasives) on bacterial layers. The peptide's antibacterial effect is equivalent to that of magnenin, cycrobin, and dermapeptin (Table 1). (Table 1). Additionally, introducing a positive charge to its N-terminus increases its antibacterial activity against Gram-positive bacteria while reducing its mild hemolytic activity [64]. Analogues with a polished secondary structure have a 25-80 percent more alpha-helical content than their stable equivalent at 40 percent CF3CH2OH / water [65]. Peroxidase causes guinea pigs' intestinal smooth muscle to contract in a post-functional isotropic way, leading to drug development [66]. (See Table 4) (See Figures 1 and 2).

Gramysterins

Gramistines are toxic peptides found in the skin secretions of soap fish Gramistes sexlinatus and Pogonoperca punctata. Pogonoperca punctata has six grammists (Pp 1, Pp 2a, Pp 2b, Pp 3, Pp 4a, and Pp 4b) however two (Gs 1 and Gs 2) in Gramistes sexlinatus [73-75]. Gramistin (Gs A-C) is an expansive range subterranean insect Queen-lytic activity on cells [76-79]. (Table 4).

Arbutrin

Arpotrine is a 49-day peptide containing a key chain of linear HGGYKPTDK amino acids [69]. It is isolated from freshwater stingray Potamotrigan Grorbigni Poison. When administered topically to the rat muscle chromaster, it causes vasoconstriction [69]. (Tables 4 and 5).

Perflon

Porvalan is a 2.0 kDa biopeptide isolated from porphyromonas orbigni. It does not differ from previously identified peptides or proteins [70]. It increases the frequency of rolling leukocytes in the mouse cremasteric muscle veins, indicating anti-inflammatory action [71]. Perflon does not only pass through biological membranes and can also be used to stimulate active transport and activity within extracellular domains [72]. (Table 4).

Hyaluronidase is a type of enzyme

There are three Nglycosylation sites in these enzymes, which have a molecular weight of 62-79 kDa [89]. All these enzymes are related to each other, but only half of them are identical [90, 91]. These substances bind to high levels of hyaluronan substrate [92]. Lionfish hyaluronidase P. volitions and P. prenatally sequence identity 99.6% and homology 72-77% with stony hyaluronidase. Five potential glycosylation binding sites have been identified in the Lionfish hyaluronidase sequences, three of which are in the Stonefish hyaluronidase [93].

Callicrin

A callicrine-like enzyme found in T. nattereri venom induces inflammation and adds to discomfort and edema. T. nattereri's poison is made up of five proteins known as Natterins, which together comprise a novel class of toxins [80, 81]. Natrin has a range of molecular weights ranging from 41.4 kDa (Natrin 4, 387 amino acids) to 5.9 kDa (Natrin 5, 387 amino acids) (Natrin P, 71 amino acids). These produce edema and have a callicreen action [82]. (See Table 4) Natrines initiate rot by separating type I and type IV collagen strands in the burdened cells [83-85]. Natrin has an unobtrusive mitigating sway, hinders leukocyte-endothelial collaborations, and brings down neutrophil collection [86]. These impacts are brought about by bad signals made by the TLR2-TLR4/Myd88 flagging course, which are interceded by vital motioning of serine/threonine phosphatase enactment and the PI3K atom [87]. When ingested quickly, fish toxin causes hemolytic, vascular, neuromuscular, skeletal, and skin rot, as well as edema, vasospasm, erythema, aggravation, intense distress or cyanosis, and tissue rot (Table 4). (See Figure 1) Toxicity in fish poisons is caused by a variety of species, each of which has a unique biological function. These stimulate neuromuscular action in muscle cells and neurons by acting on or blocking certain ion channels. Gramistin, paradoxin, epenicidin, SP-CL-5, dracotoxin, and cardiolibutin cause hemolysis by forming holes in red blood cell membranes with a diameter of up to 3.2 nm. (See Table 5)

Biological action of fish venom

TLY, a deadly toxin discovered in S. trachinis, invigorates the neuromuscular intersection to deliver acetylcholine. Extracellular Ca2 + levels invigorate the neurotoxic impacts of a few poisons, which incorporate loss of motion of the appendages, solid shortcoming, obviousness, and respiratory disappointment. It likewise forestalls the utilitarian weakness of serotonin or receptor H1 receptors, tachykinin NK1 receptors, and capsaicin-delicate tactile nerve terminals, which

represses the contractile movement of cyclooxygenase. Phosphodiesterase, corrosive phosphatase, soluble phosphatase, protein, and casein movement are on the whole present in Scotophagus argus toxin (Scatophagidae). Venom produces intense pain, edema, inflammation, and necrosis in the hunter, as well as acute injuries and local tissue damage. It causes substantial muscular damage in experimental rats' abdominal muscles (Table 6). A toxin found in many fish toxins induces red blood cell destruction. The lysis of erythrocytes is caused by hydrophilic holes in the cell membrane. SNTX, trachynilysin, and SpCTx all generate holes in cell membranes. Carotoxin is a cytolytic, agonist, and chemo-activator with the potential to trap red blood cells in rabbits [100]. Another enzyme that promotes hemolysis is PLA2 (phospholipase 2). Stone toxin induces endothelium-dependent relaxation at low doses, while P. volitional toxin produces hypotension and S. trachinase toxin causes hypertension (Table 6). On vertebrates, fish toxin creates an assortment of results, including toxicological and physiological modifications. Poisons assault an assortment of body frameworks and exercises to hinder planned hunters. It ties to receptors by means of ligand-gated channels, controls particle channels, and has three distinct kinds of direct porous activity. Poisons hugely affect the heart and circulatory framework. All fish toxins induce broad modifications suitable for application in vitro and in vivo, including the arrival of nitric oxide from endothelial cells. Smooth muscular compressions and atrial withdrawals both augment. Pelvic toxins activate the neuromuscular system as well as the cardiovascular system. Headache, vomiting, stomach discomfort, high blood pressure, hypotension, arrhythmia, stroke, seizures, collapse, and shock are all frequent adverse effects. Severe pain, swelling, sweating, ulceration, bleeding, and necrosis are the most prevalent physical signs. These poisons have systemic effects, including paralysis and hemorrhage. Neurotoxicity, inflammatory neurotoxicity, myotoxicity, coagulation interference, nephrotoxicity, and cardiotoxicity are all caused by these drugs. A poison causes the immediate inflammatory response (Fig. 1). Fish venom contains enzymes, micropeptides, and proteins, as well as non-proteinaceous compounds with a range of biological activity (Table 5).

Non-protein ingredients

Non-protein compounds are also present in fish venom. In T. viper venom, 5-hydroxytryptamine (5-HT), often known as serotonin, is a recognized nociceptive molecule [94, 95]. G. Marmoratus venom also includes a substance called 5-HT or 5-HT, which blocks the 5-HT receptor antagonist by acting directly on 5-HT receptors. Norepinephrine, but not serotonin, is found in stonefish venom [96]. S. verukosa venom has more norepinephrine than S. horida venom, but much less dopamine and tryptophan [97]. Toxins such as SNTX and VTX, for example, cause cardiovascular consequences. P. volitions venom has a non-protein poison with a molecular weight of 3.27 kDa that paralyzes its victims. [98] Acetylcholine is present in P. volitions toxin, but its role is uncertain [99].

Activity Mechanisms Fish poisons are charge transporter synthetic compounds that impede intracellular particle homeostasis by restricting to specific particle channels, siphons, carriers, and ligand-gated ionization receptors. G protein-coupled tyrosine kinase receptors and G protein-coupled tyrosine kinase receptors are likewise utilized to change optional couriers over to destructive

levels and to apply specific impacts by parts of fish toxin. Poisons enter cells by explicit homes subsequent to going through metabolic cycles and targets, for example, the mitochondria, core, protein and RNA synthesizers, and cytoskeletal networks. The excretory vessels are likewise focused on, and their standard capacities are hampered. In view of changes in underlying amino acids, different poisons communicate at unmistakable exact areas of activity. They can control or raise the movement/force of their limiting and cell-type-explicit interests. They interface distinctively with the host's optional couriers and flagging successions once they hit them. The objective area of the response still up in the air by the poison's synthetic cosmetics. Once inside the cell, poisons upset and obliterate various normal auxiliary couriers and protein kinases/phosphatase pathways (Table 4).

Cytolytic activity

SNTX, trachynilysin and Sp-CTx are scorpionoid toxins that produce pores in the cell membranes and have a stimulatory action. Carotoxin has cytolytic, viral and chemical reactions to red blood cells in rabbits, as well as additive effects [101]. (Figure 1). Paradoxin is a cationic, antimicrobial peptide that kills cells produced from red sea flatfish. Endoplasmic reticulum (ER) is involved in targeting and c-FOS activation cell death. Calcium levels increased as a result of paroxysm treatment and inhibited cellular calcium signaling from paradoxin-induced cell death [102]. (Table 6).

Proteolytic activity is the ability to break down proteins.

[112] Peptidase movement differs among the compounds found in fish toxin. Basic and corrosive phosphatases, as well as phosphodiesterase movement, are found in S. argus toxin [112]. (See Figure 1) In marine stingrays, proteolytic chemicals against casein, gelatin, and fibrinogen have been found. P. Scobina and P. Orbignons unrefined poisons show an equivalent proteolytic impact on casein [113]. Proteolytic chemicals are proteins with an extended life expectancy [113]. Both exogenous and endogenous G. marmoratus and S. horida contain these chemicals [113]. Angiotensin-changing over compound movement is additionally present in T. nattereri toxin, which serves to the fiery reaction to the poison [114]. (See Table 6) Proteolytic movement has been found in frogs T. nattereri, T. maculosa, catfish A. thalassinus, and butterfly S. argus [114, 115]. The poison of T. nattereri has been found to have a thick impact. In the fish P. heinlein, N. vigorous, and P. volitans, proteases were found (45-97 kDa by weight). The toxin of S. plumier has been displayed to proteolytically affect casein and gelatin. Fish toxin, in contrast to proteins, has a scope of compounds.

Activation of hemolytic enzymes

The hemolytic effect of fish venom varies by species, venom type, effect, and sensitivity [103]. They cause considerable discomfort in the extremities, with edema and redness as a result of inflammation in the regional lymph nodes [104-105]. (Tables 2 and 3). Raw T. Draco toxin, Dracotoxin, at 50 effective doses of 3 ng / ml, causes hemolysis of red blood cells in rabbits [108, 109]. Fish toxins may potentially hydrolyze other cell types. HeLa cells and platelets have been

demonstrated to be lost when exposed to S. Argus toxin [110]. (See Figure 1) Both thalasseprin notrea and S. horida toxin demonstrate platelet-clearing effect, but S. horida toxin does not generate appreciable hela cell death [111, 112]. Hypodite rubribinnis induces considerable hemolysis in rabbit erythrocytes, despite the fact that P. lunulata H. phospholipase is 10 times more active than A2 (PLA2), a cytotoxic enzyme contained in numerous animal poisons. [113] PLA2 proteins, on the other hand, are generally deficient in fish toxins [114-116]. Hemolytic fish toxins, on the other hand, work in a number of ways. Plotosus linatus, an eastern catfish, secretes at least one hemolysin, two cancer-causing factors, and two edema-causing factors. Around the dorsal and thoracic sting, glandular cells secreting this toxin may be detected in fish cuticles (Table 6). (Table 6).

Cardiovascular exercises

When fish toxins are administered intravenously to animals, most fish toxins can cause circulatory failure in as low as 200 g / kg. P. canis Hamilton venom (locally known as 'con major') in small doses has a beneficial inotropic effect on the hearts of frogs and rabbits, but can cause cardiac arrest and inhibit pharmacodynamic activity in large doses. Its LD50 was found to be 3.9 mg / kg. In the rat's cremaster muscle postcapillary veins, the catfish toxin C. spicii causes leukocytes to roll and stick. In the peritoneal cavity, it is the vascular p s, uterus and rat ileum. Catfish venom induces contraction of isolated guinea pig ileum, which is not inhibited by atropine or mepramine but is slightly inhibited by methyceride [118].

In doses of 30 to 100 g / animal, p. The raw venom of Maculatus stinger affects vascular permeability as well as has nociceptive and anti-inflammatory effects. Although it did not affect clotting or hemorrhage times, it did induce significant changes in CK levels and the CK-MB isoenzyme in mice (Tables 4 and 5) [119]. Toxic chemicals produced by Persian Gulf catfish (Arios thalassemus, ruble) exhibit cholinergic vasoconstrictor effect in sheep umbilical arteries and kidneys (Table 2). [120].

Neurotoxic action

Poisons from six species, transcendently cartilaginous stingrays, were found in the exploratory creatures (10-100 g/kg), including Neotrigan kuhli and Himantura toshi, Bonnie fish Platycephalus fuscus, Girella trichospidata, Mugil cephalus, and Dentex tumifranscy, neurota. The poison of P. fucus produces a hypotensive reaction, while the poison of G. tricuspidata causes a solitary hypotensive response. Poisons from N. kali, H. toshi, and P. fucus produce backhanded withdrawals in Chick Cervical Nerve Muscle (CBCNM) in a fixation subordinate way [116]. These three poisons additionally repress exogenous acetylcholine (ACh) and caracol (CCh) reactions however don't hinder the potassium chloride (KCl) channel, showing a post-synaptic activity system (Fig. 1). Poisons from G. tricuspidata, M. domes, and D. (Table 6) were excluded from the cervical neuralgia (CBCNM) arrangement.

Anti-cancer properties

When used in vitro cell culture, peroxidase usually kills cancer cells. By increasing the synthesis of c-FOS, it promotes cell death in a variety of cancer cells. Immunofluorescence indicators of cleaved cospase-3 in SCC-4 cells showed a significant increase in the expression of active cospase-3 after 24 hours of treatment with paradoxin. SCC-4 cells are also halted at the G2/M stage after being treated with peroxidase, which stifles cell development. Peroxide causes apoptosis, caspase-7 activation, and interleukin (IL)-7r production, as well as a reduction in caspase-9 control, ATF 3, SOCS3, STAT3, catholysidine, p65, and interferon (IFN) production (IFN). After 14 days of treatment, the atomic variable (NF) - B demise receptor/passing receptor flagging pathway increases apoptosis in developing mice. As a marine medication, the substance might be used to treat fibrosarcoma and oral disease (Fig. 1). (See Figure 1). In vitro, P. volitans toxin induces apoptosis in HEp2 and HeLa cells. It has anticancer properties in malignant growth cells, but has minimal impact on solid lymphocytes (Table 6). (See Table 6)

Inflammatory response

Plasmodium falciparum toxins trigger an inflammatory response in which lipid mediators (LTB4 and PGE2), cytokines (IL-1 and TNF-), and chemokines (KC and MCP-1) coordinate immune cell assignment to peripheral organs (KC and MCP-1). The structural and nociceptive mechanisms that cause severe inflammation and pain include serotonin, leukotriene, and prostaglandins (Figure 1). (See Figure 1) Non-specific cytokine inhibitors, COX-2 inhibitors, and non-selective 5-HT receptor antigens were equally effective as selective COX-2 inhibitors in reducing symptoms [121]. (See Table 6) The mucosa stimulated neutrophil recruitment shortly after injection, which was followed by macrophage infiltration. Peritoneal macrophages that have been exposed to toxins have lost their ability to develop into dendritic cells. Toxins invading the cells create this sickness. Toxins may also cause peritonitis, which is characterised by the production of cytokines (IL-6), chemokines (MCP-1 and KC), and lipid mediators in the peritoneal cavity (LTB4). CD11c sting isn't expressed in venom, and MHC Class II levels aren't high enough. The inflammatory response to fish toxins is enhanced by antigen retention in the peritoneal cavity and phagocytic cell activation [122, 123].

Immune modulating properties

Fish toxins change the kinetics of leukocyte inflow in infected mice's pathways, disrupt neutrophil transport, and diminish macrophage survival. The mending system was hurt as an outcome [140]. Fish toxin causes a hearty neighborhood fiery reaction by initiating macrophages [140, 142]. Both IL-4 and IFN-[[143] control M1 macrophage extremity. Not exclusively does nootactin impact dendritic cell action, yet it likewise impacts T-cell reactions to the Th1 aggregate [144]. (See Figure 1) They cause immunological reactions in test creatures after birth and are utilized to invigorate Th17 cell development and IL-17 creation in antibody instigated Th17 cells [144]. The poisonousness of T. nattereri plainly upholds that memory T cells are answerable for the IL-17A activity [145]. Thalassophrine public accountant fish toxin supports IL-5 creation while killing B220+ cells

[146]. Protease is used to kill nitrinins, which makes the spleen produce inborn B cells and plasma cells [147]. As a result, memory B cells produced from the germinal place partition into plasma B cells [148]. Both IL-5 and IL-17A produce a constant invulnerable globulin reaction and the arrangement of persistent immune response emitting cells in aroused tissues [149]. Moreover, the joining of antigen and IL-17A flagging is expected for the age of constant immune response emitting cells, which guarantees their lifetime [150].

Antimicrobial properties

Antimicrobial peptides (AMPs) are antimicrobial poisons that bind to microbial cell membranes and induce cell lysis. Paradoxin is an antibacterial catechin AMP that might be used as a complex anti-infection treatment. Hepsidine 1, liver-communicating antimicrobial peptide 2 (Leap-2), picidin, moronesidine, NK-lysine, and -defense are among the anti-infective chemicals specialized by S. Marmoratus. It is used to destroy microbes in hydroponics [124]. (For further information, see Tables 2 and 3.) Most type I and II Christians use bactericidal drugs to kill Gram-positive bacteria, whereas type III Christians choose protease inhibitors. Many fish species are responsible for different WAP areas of fish toxin, which are involved in a range of physiological cycles such protein barrier, bacterial death, and calcium transport resistance [125]. Epinecidin is more efficient against methicillin-resistant Staphylococcus aureus than synergistic streptomycin plus kanamycin. Antibacterial activity of AMPs is almost identical to that of a broad spectrum of anti-infective drugs, and they outperform non-peptide anti-microbials [126]. (See Table 6) (See Illustration 1)

The catalytic resistance movement inhibits the action of various physiological compounds, including toxins, proteases [127, 128], hyaluronidase, and phospholipase C [129, 130] isolated from fish such as rockfish, militaryfish, and lionfish. They also produce various metabolic and clinical adjustments [131–134], requiring a serum balance of the adverse effects of toxins [135, 136]. Fish toxins have also been found to have an angiotensin-maintaining action [137]. The N. robusta toxin also contains hyaluronidase, while the S. argus toxin contains the action of phospho (CE), soluble phosphatase (ALP), aspartate transaminase (AST), protein, and 5 nucleotides (5'- NT) [139]. (See Figure 1 and Table 6 for additional data.)

Anti-poison treatment

In terms of public health, leisure, and tourism, fish poisoning is costly. Discomfort, regional edema, and erythema begin fast, and are swiftly followed by severe necrosis. Toxicity of fish, antitoxins specific to fish Stings may be used to quickly neutralize a situation. Antivenom is thought to be a sophisticated instrument for counteracting the effects of poisons [172]. Medical therapy includes both general and specialized procedures. Antivirus software is only accessible to certain dangerous kinds, not all. Antivenomes against marine sharks and other deadly fish produced by huge sharks are in low supply. Antigen-specific antibodies and strongly related antibodies with a particular immune response may efficiently generate symptoms of fish venom-induced quick and severe inflammatory reactions. Antiviral treatment successfully neutralizes the

detrimental effects of fish toxins [172] and provides patients with life-saving protection [173]. Antitoxins that save lives are in low supply, and rural areas are disproportionately impacted [173].

Drug development using toxins

Many poisonous low-molecular-weight peptides, enzymes, and non-protein components have been discovered in fish poisons, as indicated by various exploration. These parts associate with different huge particles, tie to particular receptors, and make physiological and natural results through intracellular flagging by means of assorted entryways [151, 152]. Fish toxin peptides and proteins are pharmacologically dynamic and are taken advantage of in helpful advancement [153, 154]. (See Tables 4 and 6 for additional data.) (See Figures 2a and 2b). A huge number of creature toxin have effectively been transformed into drugs [155]. Researchers are using toxic bionic informatics data from various animal poisons to generate novel and more effective medications and diagnostics (Fig. 1a, 1b, 1c) [156, 157]. These medicines reduce pain by targeting receptors and ion channels and are fast-acting and highly selective [158, 159]. These medications have been demonstrated to be equally effective as antidepressants, analgesics, and neuromodulators in the treatment of depression and pain. [160] Furthermore, these poison-based medications have certain disadvantages since, when taken as a drug in the human body, they often lose their potency and precision. These medicines are selective and may influence other targets due to their limited effectiveness. It is impossible to prevent unintended negative consequences after using it (Tables 4 and 6). Because of its huge size, it does not pass the blood-brain barrier like tiny synthesized compounds. They may, however, simply avoid it. The majority of these toxin-containing medications are peptides, which cannot be taken orally and may be lethal if consumed [161]. The bioinformatic features of natural poisons change during drug (toxin) production, resulting in substantial physiological repercussions [162]. It also changes binding receptors and communication pathways, resulting in the innate immune response of the patient [163]. Natural poison venom interacts differently with physically crucial molecular targets than templates, impacting the intricate functioning of organisms otherwise [164, 165]. Toxin-containing analgesics [166] and other treatments [167] are often made using toxin-containing medicines. (See Figures 2a and 2b). Toxin structures are also required, as are collaborations across the domains of biochemistry, pharmacology, and immunology to advance knowledge and produce new ideas. Fish venom peptides have been employed to generate novel medications [169], as well as pharmaceuticals for immuno diagnostics, poisons, and therapeutic reasons [170, 171]. (See Figures 2a and 2b). The poison templates may be utilized to develop new targeted, less dangerous therapeutic medications by making tiny structural modifications to them. Fish venom has a wide range of biomedical applications, including the development of biopesticides and the control of a wide range of agricultural crop pests (Figs. 2a and 2b).

Conclusion

Fish toxins are very specific because they have a wide range of structures and functions and belong to many families. Toxins and proteolytic enzymes, mostly small protein toxins and non-protein compounds, are abundant in fish venom.

These components are potent toxins that cause a variety of clinical and pathophysiological effects. Fish poisons have a variety of biological actions, such as not being humorous and causing extreme pain when taken. Furthermore, biological data on fish toxins can be used to learn more about the evolutionary relationships between toxic organisms and their diet. Highly supplemented antigen-specific antibodies are produced for the rapid neutralization of fish poisoning, which reduces the symptoms caused by fish poisoning and the acute inflammatory response.

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