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Pharmacological Potentials of Scorpaenidae Fish Venom

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Abstract: The venomous property of certain fishes have been recognized for many years; however scientific investigators have begun recently in finding the pharmacological potential of their venom. A number of venomous fishes have been investigated to explore their biological activities and therapeutic potential. Venomous fish possess wide range of toxins for predation and defense. The discovery of toxins or metabolites from fish venom has been increased significantly. Scorpaenidae family includes the world's most venomous fish species. Their venom represents an incredible source of biologically active substances which affect vital physiological function in different animal model. The venom of these fishes is diverse and chemically complex in nature. The envenomation caused by these fishes are responsible for severe pain, edema and other complications but their venom contain many pharmacologically active component. Many toxins isolated from crude venom have been reported to be affecting cardiovascular, neuromuscular systems. They are also responsible for hemolytic activities. This review describes the pharmacological potential of Scorpaenidae venom that can be useful as research tools or lead compounds for further drugs development.

Keywords: Scorpaenidae, Venom, Cardiovascular, Neuromuscular, Hemolytic

Introduction

Venomous and poisonous animals are also found in aquatic environment in large number. Among these, venomous fish attracts special interest, since they represent more than 50% of venomous vertebrates and are often involved in human accidents [1, 2, 3]. Russell, in 1996[4] reported around 200 species of marine fish, including stingrays, scorpionfish, zebrafish, stonefish, weeverfish, toadfish, stargrazers and some species of shark, ratfish, catfish, sugeonfish and blenny which are known or suspected to be venomous. But this number of fish species clearly underestimates the number of venomous fishes implied by the phylogenetic distribution of venom among ray-finned fishes[3]. The most dangerous, venomous fish known belong to Scorpaenidae family and, according to the venom organ structure, they are divided in to three groups typified by different genera: *Pterois* (lionfish), *Synanceja* (stonefish) and *Scorpaena* (scorpionfish)[5].

Marine fish belonging to family Scorpaenidae cause severe injuries and sometimes death in humans around the world[6]. Studies on the epidemiological and clinical aspects of envenomation caused by these fishes focused mainly on lionfishes and stonefishes [7]. However, there are few reports of injuries caused by the venom ejected by the venom apparatus of *Scorpaena* [8].

Three populations are at higher risk for spiny fish envenomation: fishermen sorting the catch from

nets, waders, and aquarists etc. Lionfish (genus *Pterois*) are common to home aquariums and responsible for envenomation when mishandled. At least eighty species of the family scorpaenidae are said to possess venom apparatus. Fishermen and swimmers are the main victims of scorpionfish envenomations which occur as a result of contact with sharp dorsal pelvic or anal spines and stonefish envenomation is still an occupational hazard in many areas of the world [9]. The distribution and number of venomous fish belonging to Scorpaenidae family has been listed in Table 1.

Table 1: Occurrence and number of venomous Scorpaenidae fish

Venomous species	Occurrence	World	India
Scorpaenidae (Scorpions and rock fishes)	Tropical and Temperate seas	185-200	58
Sebastidae (Stingfishes)	Atlantic, Indo-Pacific	115-130	31
Apistidae (Waspfishes)	Indo-west Pacific	3	1
Synanceiidae (Stonefishes)	Indo-Pacific	36	5
Tetrarogidae (Sailback scorpionfishes)	Indo-west Pacific	42	10

Source: Adapted from Khora, 1986[54]; Smith and Wheeler, 2006[3]

SCORPAENIDAE VENOM APPARATUS AND ENVENOMATION

All the fishes of family Scorpaenidae have 11- 17 rays or spines in the dorsal fin (in the genus *Scorpaena*, there are 12-13 rays) [10]. The dorsal spines of Lionfishes are slender and long and contain small venom glands. Whereas, the spines of scorpionfish are strong and short, and the venom glands are more developed. The spines of stonefish are very thick and short with highly developed venom glands [11]. The venom apparatus of the Scorpaenidae is constituted by elongated venom glands in the anterolateral grooves of the spines in the dorsal, pelvic and anal fins without an excretory duct in the case of lionfish and scorpionfish while in the case of stonefish, there are highly developed longitudinal paired glands with well-developed duct like extensions [8]. It is thought that venom apparatus evolved relatively recently in the development of venomous fish, because while fish are on a higher level of development than some other groups of venomous creatures (e.g. spiders), their venom apparatus are much more primitive relying on a completely involuntary mechanical action, rather than a voluntary expulsion of venom [12].

Table 2: *Presentation, Complications and Management of Lionfish and Stonefish envenomation*

Fish	Common sign and symptoms	Complications	Treatments	Antivenom	References
Lionfish	Weakest among others in Scorpionfish family; sharp, intense pain that radiates to other area beyond the puncture site	Erythema, pallor, local necrosis, vesicle formation	i) All the spines must be removed and the affected limb should be cleaned. ii) Hot water immersion is done to relieve acute pain. iii) In addition supplemental local or oral analgesia may be administered. iv) No need of antibiotic; even though antibiotics are required if any sign of infection or if Gram positive bacteria are noted	Specific antivenom is available for the different species of scorpionfish and helps in relieving the pain and systemic effect of envenomation	15-18
Stonefish	Edema, muscle weakness, syncope, dyspnea, headache and hallucinations	Hypotensive, Myotoxic and Neurotoxic effects			

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Venom is delivered when spines pierce the tissue of the victim, glands get compressed, the integumentary sheath enclosing the spine is ruptured and the venom enters the wound [13]. The envenomation caused by these fishes reported various symptoms including intense pain, swelling, ulcers, skin damage and rarely death associated with bacterial infection [14]. It may take a few days or several weeks for recovery from the local effects (Table 2). Hot water immersion or heat therapy for few minutes can be provided as first-aid.

SCORPAENIDAE VENOM

Like terrestrial venomous animals, fish venoms also contain a variety of pharmacologically active component. A very less research has been done on venomous fishes, though the symptoms produced by their envenomation are severe. It may be due to less threat associated with marine creatures in respect to terrestrial animals and also due to extreme instability and scarcity of the venom [19]. The venom produced by these fishes is diverse and chemically complex in nature. Fishes of the family Scorpaenidae contain heat labile venom which is common in all species but with different potency and possess cardiotoxicity and neurotoxicity. The proteinaceous nature of venom is still not well characterized. There are few studies on the venom of the scorpionfishes (*Scorpaena*). The venom is highly heat labile, the lethal property being associated with the proteinaceous fraction of venom having molecular weight more than 50,000 and less than 800,000. This separated fraction is more lethal than crude venom [20]. It is reported that the fluid ejected from the blister caused by Lionfish sting produced experimental platelet aggregation [21].

Three main toxins have been isolated from various species of stonefish: stonustoxin (SNTX), verrucotoxin (VTX), and trachynilysin (TLY). Stonustoxin (SNTX), from *S. horrida,* has 2 subunits, α and β (71,000 and 79,000 Daltons, respectively) [22] (Table 3). It induces formation of hydrophilic pores in cell membranes. Toxicity in animals includes hemolysis, local edema, vascular permeability, platelet aggregation, endothelium-dependent vasodilation, and hypotension. It is described that the pronounced effects of stonefishes venom are on the cardiovascular and neuromuscular systems, with hemolytic and hyaluronidase activities [23]. Stonustoxin (SNTX) which is toxic protein with lethal action has been identified which causes severe hypotension. It is also found possessing high cholinesterase, acid and alkaline phosphatase and phosphodiesterase activity [7].

Table 3: *Toxins from Scorpaenidae venom and properties*

Species of Scorpaenidae	Toxin	Structural properties	Active components	References
P. volitans (Firefish)	Non-proteinaceous toxin	327 Da	Acetylcholine or cholinomimetic agent	24-29
S. verrucosa (Reef stonefish)	VTX	Four subunits 2α (83 k Da) and 2β (78 k Da)	All three species of stonefish contain catecholamines as well as other enzymatic activities	
S. horrida (Indian stonefish)	SNTX	Two subunits α = 699 AA, β = 702 AA		
S. trachynis (Estuarine stonefish)	TLY	158 k Da		

Source: Adapted from Church and Hodgson, 2002[19]

EFFECTS ON CARDIOVASCULAR SYSTEM

Piscine venoms have potent activity. It is observed that the venom of the Indian stonefish (*S. horrida*) produces marked cardiovascular changes in experimental animals [30] and also found that the cardiovascular pharmacology of *S. trachynis* venom have produced results that have differed from those obtained by researchers using the venoms of *S. horrida* and *S. verrucosa* [31]. It is found that lyophilized venom produced endothelium-dependent relaxation in vascular smooth muscle of the rat [28]. The same effect has also been observed in the lethal fraction of *S. horrida* venom i.e., stonustoxin[32]. They also found that stonustoxin (SNTX) at low concentration responsible for causing endothelium dependent relaxation and at high concentration; it shows endothelium independent contraction[33]. Both vascular and non-vascular smooth muscles are affected by many fish venoms.

Clinical and epidemiological studies on the *S. plumieri* venom shows pronounced cardiovascular effects[8]. The scorpionfish (*S. plumieri*) at sub-lethal doses (14-216 µg/Kg) in the anesthetized rat produces hypertensive response. While at higher lethal doses (388 µg/Kg), this response is followed by hypotension, a visible respiratory difficulty which ends up in respiratory arrest[34]. It is concluded that the respiratory collapse is actually, a consequence of cardiovascular collapse. The effect of piscine venoms on isolated vessels is found to be concentration dependent. It is found that *S. trachynis* venom produces a relaxation at low concentration and at high concentration produces contractile effect[28]. The venom of the lionfish *P. volitans* produces a marked hypotensive effect in anesthetized rabbits[35].

Church and Hodgson in 2001 worked on *P. volitans* venom to determine its cardiovascular effects as well as to elucidate the mechanism of action of venom. Venom produces dose and endothelium-dependent relaxation in pig coronary artery [36]. Cardiovascular activity of *Scorpaena plumieri* venom was investigated by both *in vivo* and *in vitro* model [34]. The results of their experiment shows that, in the anesthetized rat, the scorpionfish venom produces a remarkable hypertensive response at sub-lethal doses (14-216 mg/kg), follows by hypotension at higher or lethal doses (338 mg/kg), respiratory difficulties are also visible which ends up in respiratory arrest. Stonefish envenomation symptoms are similar to soldierfish envenomation symptoms which include severe burning pain, local swelling, sweating, nausea and loss of perceptiom[37]. As the envenomation symptoms of soldierfish and stonefish share similar pharmacological activity and qualitative similarity, so the effectiveness of antivenom (raised against the venom of stonefish; *Synanceja* spp.) in neutralising the cardiovascular effects of soldierfish (*G. marmoratus*) is investigated[2] and it is found that the *Synanceja* antivenom is effective in neutralising most of the cardiovascular activity of *G. marmoratus* venom extract *in vitro* and *in vivo* both. This suggests that the *Synanceja* antivenom may have potential which can be used in severe cases of envenomation caused by *G. marmoratus*.

EFFECTS ON NEUROMUSCULAR SYSTEM

Though the symptoms of *Synanceja* envenomation are mostly cardiovascular in nature, some symptoms related with neuromuscular effects have also been reported[38]. Electrophysiological and electron microscopic examination of isolated murine and

frog nerve-skeletal muscle preparations exposed to various concentration of stonefish venom shows the neuromuscular toxicity of the venom. It is observed that the low concentrations of venom acts presynaptically (Na^+ channel-independent) while higher concentrations of venom acts presynaptically and postsynaptically both by causing release and depletion of neurotransmitter from the nerve terminal[39]. This neurotransmitter release is found to be resistant to blockade of Na^+ channel and also resistant to botulinum toxin. This indicates the release of acetylcholine via a non-exocytotic mechanism.

The crude *S. trachynis* venom is found to increase the mean number of quanta released per nerve stimulus and produces markable damage to nerve and muscle cells, as well as preventing synaptic recycling at higher concentrations in the frog stimulated cutaneous pectoris nerve-muscle preparations. From these observations, it is concluded that the crude venom of *S. trachynis* is responsible for neurotoxic effect by releasing massive neurotransmitter at low concentrations and causes muscle and nerve damage at higher concentrations [39]. In the same study it is found that the lethal fraction, TLY of *S. trachynis* crude venom is responsible for neuromuscular effects *in vitro*. Also, TLY has been shown to induce Ca^{+2} entries in to adrenal chromaffin cells and also affecting intracellular Ca^{+2} stores and increasing Ca^{+2} dependent catecholamine releases[40]. Signs of neurotoxicity have also been observed both in mice and other fish by *Pterois volitans* venom[24]. It is observed that *P. volitans* venom extract derived from its spine tissue decreases the heart rate and force of contraction in isolated clam and frog hearts. These actions are found to be due to presence of micromolar concentrations of acetylcholine in the extract. The hydrolysis of acetylcholine by exogenous acetylcholinesterase does not affect the venom toxicity as well as the heart function. This indicates that the venom is interfering with neuromuscular transmission rather than the muscle itself. Unaffected sodium channel blockade suggests that the toxin has an effect at the nerve terminal rather than interfering with synaptic transmission[41].

The direct evidence of trachynilysin, isolated from *S. trachynis* venom is observed, which increases the spontaneous quantal acetylcholine release in *Torpedo* nerve-muscle preparations[42]. It is found that the lyophilised venom produces endothelium-dependent relaxation in the vascular smooth muscle of the rat. The same effect has also been observed in studies using stonustoxin (SNTX), the lethal fraction of *S. horrida* venom[32]. The venom of *Scorpaena guttata* causes a biphasic response in paired atria consisting of an inotropic decrease due to activation of muscarinic receptors and follows by inotropic increase due to activation of adrenoceptors [43]. It is known that the cardiovascular effects associated with stonefish envenomation are life-threatening[37], however it is not known whether the lethality of stonefish venom is due to the cardiovascular effects, or to neuromuscular toxicity. Studies conducted on *S. verrucosa* crude venom shows neurotoxic effect when the venom is administered i.c.v. to rats. This effect is found to be different from the VTX, the lethal toxin isolated from *S. verrucosa* venom. This fraction is unable to produce the same severe neurotoxic effect as produced by crude venom when administered i.c.v. to rats suggesting the presence of at least one other active component in *S. verrucosa* crude venom[44]. SNTX similar to TLY produces a contracture followed by a decrease

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in electrically-evoked twitches in the mouse hemi-diaphragm and chick biventer cervicis muscle as well. It is concluded that the contraction produced by SNTX is not dependent on the release of acetylcholine but rather Ca^{+2} release and / or activation [33].

G. marmoratus envenomation in mice leads to neurotoxic effects which include paralysis of hind limbs, muscular weakness and at higher doses lead to coma and respiratory cessation. Also, *G. marmoratus* venom reduces the response of skeletal muscle to nerve stimulation but the mechanism involved in this is not studied [45]. Studies conducted by Church et al., 2003 [46] on the venomus fishes of the family scorpaenidae show for the first time that the crude venoms of *G. marmoratus* and *P.volitans* produce contraction in the chick biventer cervicis muscle. They also find that all three crude venoms produce an increase in intracellular Ca^{+2} in murine cortical neurons. The increase in Ca^{+2} is thought to be mediated via the formation of non-selective cationic pores in the cell membrane and is dependent on the entry of extracellular Ca^{+2}.

HEMOLYTIC ACTIVITIES

Cytolytic toxins are well known for their ability to kill cells. Fish venoms have hemolytic activity. The stonefish (*Synanceja verrucosa*) crude venom is found to be highly hemolytic to rabbit erythrocytes but the activity is reduced with time even when the venom is frozen. The crude venom is also purified and verrucotoxin is isolated by DEAE and hydroxyapatite chromatography. Verrucotoxin is found to be lethal and cytolyitc [47]. Neoverrucotoxin (neoVTX) is a proteinaceous toxin obtained from the venom fluid of *S. verrucosa*, has hemolytic and lethal activities and is inhibited by anionic lipids [48]. The venom of other stonefish *Synanceia trchynis* is also studied. The venom contains a cytolytic toxin which is antigenic and precipitated by ammonium sulphate. The toxin is found to be potent but narrow-spectrum in action which is lytic for erythrocytes of rabbit, dog, rat and guinea pigs *in vitro* but it is totally or largely inert against the erythrocytes of sheep, cow, human, monkey, mouse, goat, horse, burro and cat (Table 3). The hemolytic activity of venom does not get separated from its lethal and vascular permeability-increasing activities by fractionation of venom using molecular sieve fast protein liquid chromatography and isoelectric focusing. These activities of venom are found to be sensitive against heat and protease treatment[50]. *P. volitans* venom has been found to possess hemolytic activity and is highly selective to rabbit erythrocytes [51]. Stonustoxin (SNTX), purified from the crude venom of stonefish (*Synanceja horrida*) has potent hemolytic activity. The pore forming property of stonustoxin was examined by osmotic protection assay. It is found that the SNTX causes the lysis of erythrocytes by the formation of hydrophilic pores in the cell membrane. In the case of SNTX, positively charged lysine and arginine residues are used where the modification of positively charged side chain shows the inhibition of hemolytic activity of SNTX. Also the hemolytic activity of SNTX is competitively inhibited by various negatively charged lipids[51]. It is demonstrated that the reduction in number of free tryptophan residues is responsible for impairing the hemolytic activity of SNTX and it can be correlated with other toxins that require tryptophan residues for cytolytic activity[52]. The proteolytic enzymes are found to be present in the venom of *S. plumieri* responsible for hydrolyzing other bioactive proteins [53].

Table 4: Hemolytic Activity of Scorpaenidae venom (+++: high hemolytic activity, ++: medium activity, x: no evidence of hemolytic activity, -: data deficiency)

Scorpaenidae Fish	Rabbit	Rat	Human	Mouse
S. horrida (SNTX)	+++	++	x	x
S. trachynis (TLY)	+++	++	x	x
S. verrucosa (VTX)	+++	-	-	-
P. volitans	+++	-	-	-

Source: Adapted from Church and Hodgson, 2002[19].

Conclusion

Many cases of scorpaenidae envenomation have been reported in different parts of the world. Fishes of the family scorpaenidae are responsible for severe injuries but their venom contains active components which are of pharmacological importance. Scorpaenidae venoms have been recognized as potential source of pharmacological agents and physiological tools. Their venom interacts with physiologically important molecular targets and affects the vital function of organisms. In most cases, toxin present in venom is responsible for physiological effects. Scorpaenidae venom produces distinct cardiovascular changes. Stonustoxin is responsible for causing endothelium dependent relaxation at low concentration and shows endothelium independent contraction at high concentration. *P. volitans* venom produces hypotensive response whereas *S. trachynis* venom produces hypertensive response. The lethal toxin of *S. trachynis* venom (TLY) is responsible for the release of acetylcholine from the neuromuscular junction. Some of the toxins have neurotoxic effects which includes paralysis of hind limbs, muscular weakness and at higher doses causes coma and respiratory failure. Many of the fish venoms contain toxin responsible for erythrocyte lysis. The mechanism behind erythrocyte lysis by SNTX is through the formation of hydrophilic pores in the cell membrane. *P. volitans* hemolytic activity is found to be selective to rabbit erythrocytes. SNTX activity gets altered as the numbers of tryptophan residues get decreased. Scorpaenidae fish venom possess different properties which can be utilized for research tools and potential drug development.

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