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Inflammatory and Erectile Dysfunction (Impotence) Treating Potential of Lionfish Venom

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ABSTRACT

In this study, we are presenting the toxicological effects of invasive species P. miles that were observed in the northeastern Mediterranean and the Mersin coastal zone. Based on the blood test results and physiological changes, we interpreted the physiological effect of the venom on the victim. Our study group made observations, certain blood as well as physiological tests to interpret the effect of the venom on the victim. The patient's blood amounted to an immune response that had an inflammatory character rather than an allergic reaction based on the changes in the white blood cell content. Moreover, the patient had signs of muscle tissue injury as well as arrhythmia. The venom had erectile function increasing activity on the victim who was in line with the previously reported effect of lionfish venom at the intracellular level that also overlaps with the activity of Sildenafil. Our study suggests potential erectile dysfunction (impotence) treatment applications of the lionfish venom and is, to our knowledge, the first study to report and interpret such a potential of the venom.

K E Y W O R D S: Devil firefish**,** *Pterois miles,* Erectile Dysfunction, Impotence, Inflammation, Muscle Injury.

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1. Introduction

With the construction of the Suez Canal in 1869, the Mediterranean Sea has been under a period of constant change. Many invasive species have entered to the Mediterranean Sea and became preys or predators (Zenetos et al., 2012). Besides that, the seawater temperatures have been increasing all over the world throughout the years. These factors have accelerated the process of tropicalization of the Mediterranean Sea. Lionfish species; *P. volitans* (Linnaeus, 1758) and *P. miles* (Bennnet, 1828) are the last species that ended up in the region due to this process (Kletou et al., 2016).

Lionfish are one of the invasive species and are observed more in the western Atlantic than their native regions. In just two years, they became the dominant predator over the native reef fishes and decreased the abundance of reef fishes by 65 %, affecting more than 40 prey species (Green *et al.*, 2012).

Devil firefish, *P. miles* was observed in the Mediterranean Sea for the first time in Israel in 1991 (Golani & Sonin, 1992). The second record was from Lebanon in 2012 (Bariche *et al*., 2013). In 2014, two more specimens were captured in Cyprus and another one in Turkey. In 2015, two more species were observed in Cyprus and another one in Rhodes in Greece (Turan et al., 2014; Oray et al., 2015; Crocetta et al., 2015; Iglésias & Frotté, 2015). In addition to these sightings, many cases were recorded from the South of Turkey (Yaglıoglu & Ayas, 2016), which shows the migration tendency of the lionfish to the Aegean Sea (Turan & Öztürk, 2015).

Pterois miles exist within the tropical waters of the Persian Gulf, Indian Ocean (Wright, 1988), Red Sea, South Africa, south of Port Alfred, and east of Sumatra, Indonesia (Fricke, 1999). This species is demersal that is associated with reef and invasive alien species in the Atlantic Ocean that dwell in 60 m depth (Sommer *et al.*, 1996). It lives in coastal waters (Kuiter & Tonozuka, 2001), and its fin spines are venomous and can lead to death. *P. miles* is a carnivorous species and reaches a total length of 35 cm (Sommer *et al.*, 1996).

In this study, we are presenting the inflammatory and erectile dysfunction eliminating/ aphrodisiac potential of lionfish venom. Based on a case at the east Mediterranean coast of Turkey, our study group made observations, certain blood as well as physiological tests to interpret the effect of the venom on the victim. This study aims to present the toxicological effects as well as pharmaceutical potential of invasive species, P. miles, that were observed in the northeastern Mediterranean and the Mersin coastal zone. Based on the blood test results and physiological changes, we interpreted the physiological effect of the venom on the victim.

2. Materials and Methods

Case Report

On 5 May 2019, 07:00 a.m., the victim was collecting trammel nets from his fishing boat, approximately in 55-meter depth. In his net, he saw a fish (*Pterois miles*) that he had never seen before and wanted to rescue the fish while it was alive. While the fish was struggling in the net, four dorsal spines penetrated to his left-hand palm. As he withdrew his hand, he noticed the bleeding and felt a burning sensation. Almost immediately, the pain was extremely intolerable. Within a minute, the pain spread throughout his body. He was writhing and could not standstill because of the pain. He could arrive to the hospital only one hour after the sting. His hand became twice as big. When he arrived to the hospital, a series of painkillers and serum were given to the victim. After 20 hours in the hospital, his pain started to decrease, and his health status became normal. He has been kept under observation for four days in the hospital to ensure that he has been fully recovered from the poisoning. After the sting, there were spontaneous contractions in his arms that continued for three days. He reported that after 20 days of the sting, he still felt slight paresthesia in his arm.

3. RESULTS

A male patient at the age of 42 was hospitalized after interaction with the venomous spines of a lionfish at the Erdemli region of Mersin, Turkey. Afterward, the patient received medication starting from the first day of his arrival to the emergency room at the hospital on 05.05.2019 until 08.05.2019.

He received the medications indicated in Table 1. He had the following symptoms: sharp pain, edema, and erythema in the region. These are indications of the flow of white and red blood cells into the region, and pain is associated with the inflammatory response in the region (Chen et al., 2017). His ECG was abnormal, which indicated arrhythmia. When his blood content was measured over the time course as indicated in Table 2, most of the values were at normal ranges except for a PTT, Creatine Kinase, CRP, SedPar1, Phosphorus, Glucose, Calcium, and Chloride. The patient had decreased aPTT, which is correlated with the acute inflammatory response.

Table 1. List of medications applied to the patient

Date	Medications
05.05.2019	Lidocaine hydrochloride (Local anesthetic) Paracetamol (Pain killer) Tenoxicam (Anti-inflammatory agent) Ceftriaxone (Anti-biotic) Dextrose (Sugar source to enable energy)
06.05.2019	Lidocaine hydrochloride (Local anesthetic) Paracetamol (Pain killer) Tenoxicam (Anti-inflammatory agent) Ceftriaxone (Anti-biotic) Dextrose (Sugar source to enable energy)
07.05.2019	Lidocaine hydrochloride (Local anesthetic) Paracetamol (Pain killer) Tenoxicam (Anti-inflammatory agent) Ceftriaxone (Anti-biotic) Dextrose (Sugar source to enable energy)
07.05.2019	Lidocaine hydrochloride (Local anesthetic) Paracetamol (Pain killer) Tenoxicam (Anti-inflammatory agent) Ceftriaxone (Anti-biotic) Dextrose (Sugar source to enable energy)

Table 2. Changes in blood content

Date	Stayed at Normal Levels	Substantially Decreased	Substantially Increased
05.05.2019	ALT AST Creatinine K Na PTZ Albumin Urea Alkaline Phosphotase Amilase Total Bilirubin GGT Uric acid	aPTT	Creatin Kinase CRP SedPar1 Phosphorus Glucose Calcium Chloride
06.05.2019	ALT AST Creatinine K Na PTZ Albumin Urea Alkaline Phosphotase Amilase Total Bilirubin GGT Uric acid	aPTT	Creatin Kinase CRP SedPar1 Phosphorus Glucose Calcium Chloride
08.05.2019	ALT AST Creatinine K Na PTZ Albumin Urea Alkaline Phosphotase Amilase	aPTT	Creatin Kinase CRP SedPar1 Phosphorus Glucose Calcium Chloride

	Total Bilirubin GGT Uric acid		

Moreover, he had increased levels of phosphorus and chloride that have been associated with kidney diseases, and in this case, it is probably related to the changes in the blood flow and filtration due to the inflammation, edema, abnormal ECG and how kidney responded back to these complications. Increased creatine kinase and CRP levels are associated with muscle tissue injury. Lionfish venom is known to activate and paralyze the muscle cells through an increase in intracellular calcium level (Mouchbahani-Constance et al., 2018; Schultet al., 2017; Badillo et al., 2012). Probably due to this overactivity of muscles there was an increase in need of glucose as well as calcium that should be available to the muscle cells. Hence, there was a substantial increase in blood glucose and calcium levels, as well. Moreover, Sed Par 1 was increased in the patient, which also indicates an inflammatory response (Table 2). Lionfish venom is known to activate the inflammatory pathways, and this was obvious by an increase in white blood cell percentage on the first day of the incident, as indicated in Table 3 (Mouchbahani-Constance et al., 2018; Schultet al., 2017; Badilloet al., 2012). After receiving the medications, the patient's symptoms were alleviated, and this was reflected as normalization of white blood cell percentages on 08.05.2019 and decreased levels of Neutrophil percentages (Table 3). Eosinophil and lymphocyte levels were decreased (Table 3). Probably the anti-inflammatory medications were effective in decreasing the inflammatory response after two days. Decreased white blood cell numbers and neutrophil percentages after the treatment indicate that the inflammatory response was most probably associated with acute and innate immune responses rather than allergic basophil and eosinophil based or adaptively mphocyte based responses (Table 3) (Turveya & Broide, 2010; Marshall et al. 2018; Chaplin, 2010).

Table 3. Changes in blood cell numbers and percentages.

Date	Stayed at Normal Levels	Substantially Decreased	Substantially Increased
05.05.2019	RBC Basophil Eosinophil Hgb HCT Lymphocyte Neutrophils Monocytes MCH MCHC MCV RDW-SD RDW-CV PCT RDW MPV Platelets	-	White blood cells (Almost doubled)
06.05.2019	RBC Basophil Eosinophil Hgb HCT Lymphocyte Neutrophils	-	White blood cells (Almost doubled)

	Monocytes MCH MCHC MCV RDW-SD RDW-CV PCT RDW MPV Platelets		
08.05.2019	RBC White blood cells Basophil Hgb HCT Monocytes MCH MCHC MCV RDW-SD RDW-CV PCT RDW MPV Platelets	Neutrophils	Eosinophil Lymphocyte

Moreover, the patient had increased erection according to his personal records. This situation suggests that venom's effect on the victim leads to increased erection rate/duration and might imply erectile dysfunction (impotence)treatment potential of venom if used at appropriate dosages. Lionfish venom is known to increase the nitric oxide levels and intracellular calcium levels, both of which can positively affect the erection (Mouchbahani-Constance et al., 2018; Schultet al., 2017; Badillo et al., 2012). Sildenafil is a marketed drug for men with erectile dysfunction (McCullough, 2002). It is known to act through increased cGMP pathway activity and elevated NO levels (McCullough, 2002). cGMP pathway is associated with increased intracellular calcium levels (Kapakos et al. 2010). Therefore, most probably, the venom of lionfish has a similar mechanism of action as that of Sildenafil to induce erection (Mouchbahani-Constance et al., 2018; Schult et al., 2017; Badillo et al., 2012; McCullough, 2002; Kapakos et al., 2010).

4. DISCUSSION

Lionfish is a successful invasive species because of its characteristics, which are anti-predatory venomous defenses, early maturation, reproduction, and its dominance over the native prey species. Also, the overfishing of native predators helps lionfish to settle in the new areas (Côté et al., 2013).

Lionfish are slow-moving and can easily be collected by the divers. If a protective approach is needed against the impacts of the lionfish, early detection and collecting them are the first defensive actions as we know from the western Atlantic experience (Morris et al., 2009). Furthermore, Kleteo et al. (2016) stated that consuming the lionfish is safe if its venomous spines are removed. In furtherance with this information, the study by Ayas et al. (2018) was about determining the chemical composition of P. miles and also to determine heavy metal (Zn, Fe, As, Cu, Pb, and Cr) levels in their tissues and the mechanism of the accumulation. Moreover, it is concluded from this study that while lionfish muscle tissue has high minerals, protein, trace elements, and unsaturated fatty acid content, the level of heavy metals was not a range to prevent human consumption.

In this case report, we interpreted the blood test results and physiological changes of the victim who got poisoned by lionfish venom. The results suggest that the patient suffers from inflammatory responses and muscle tissue injury. Moreover, the patient experienced the venom-induced increased erection rate. Based on the observation of previous studies

with venom's intracellular effects, we could interpret that the observed effect is similar to that of Sildenafil inside the muscle and epithelial cells (Mouchbahani-Constance et al., 2018; Schultet al., 2017; Badillo et al., 2012; McCullough, 2002; Kapakos et al. 2010; Bogdanoff et al., 2013) These changes led to increased erection rate in the victim. Although lionfish is consumed due to its aphrodisiac effect, its venomous parts are removed before its consumption (Mouchbahani-Constance et al., 2018; Schultet al., 2017; Badillo et al., 2012; McCullough, 2002; Kapakos et al. 2010; Bogdanoff et al., 2013). Based on the observations, in this case, we can conclude that probably trace amounts of its venom remains on the meat during consumption hence it triggers an aphrodisiac reaction by inducing erection (Mouchbahani-Constance et al., 2018; Schult et al., 2017; Badillo et al.,2012; McCullough, 2002; Kapakos et al., 2010; Bogdanoff et al., 2013). For the first time to our knowledge, erectile dysfunction (impotence) treatment potential of lionfish venom is reported by this study. Previous studies reported lionfish consumption's aphrodisiac effect; nevertheless, the reason behind it was not elaborated (Bogdanoff et al., 2013). Observations of this case report links the observed aphrodisiac effect of lionfish consumption to its venom. Probably during consumption, a low dose of venom is also taken by the consumers, which in turn leads to aphrodisiac effect and increased erection rate.

5. CONCLUSION

The present study suggests potential erectile dysfunction (impotence) treatment applications of the lionfish venom. Our study group will further analyze these effects *in vitro* at the intracellular level in order to fully decipher the venom's mechanism of action. This information and proper dosage calculations will enable its use in the drug industry.

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