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An Overview on the Worlds Dead Liest Poison (Palytoxin and its Analogs)

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Abstract: ***Palytoxin is a marine toxin found originally in soft corals Palythoa species of the Pacific Ocean. It is a thermostable, non-protein, coronary vasoconstrictor that leads to death by diminishing the supply of O2 to the Myocardium. Several analogs of PTX or PTLX such as Ostreocin-D, Ovatoxin are found in several dinoflagellates and other marine species such as Crabs (Demania reynaudii) and Smoked Fishes (Decapterus macrosoma) found in same ecological regions. Toxicological studies of PTX showed low lethal dose values in different mammals revealing the acute toxicity due to different routes of exposure. On exposure to PTX, symptoms such as Rhabdomyolysis (high dose), Na+- K+ pump and heart failure & other symptoms including abdominal cramps, vomiting, bradycardia, etc. are seen in Pescatarians. There is no particular antidote for the PTX compounds, but these compounds can be neutralized by the household bleach solution. Activated Carbon absorbed 99.7% of palytoxin in aquarium waters. In this paper, we review the current knowledge on Palytoxin & its analogs. In recent years, many methodologies have been described for the development of new techniques for the detection of palytoxin based on LC-MS/MS and a bio-technique Immunoassay.***

Keywords: marine toxins, palytoxin, Ostreocin, ovatoxin, dinoflagellates, rhabdomyolysis, LC-MS-MS, immunoassay.



(a) (b)

Fig 1 : Soft corals of Palythoa Species; (a) colony of *Palythoa toxica* (b) colony of *Palythoa grandis*

I. INTRODUCTION

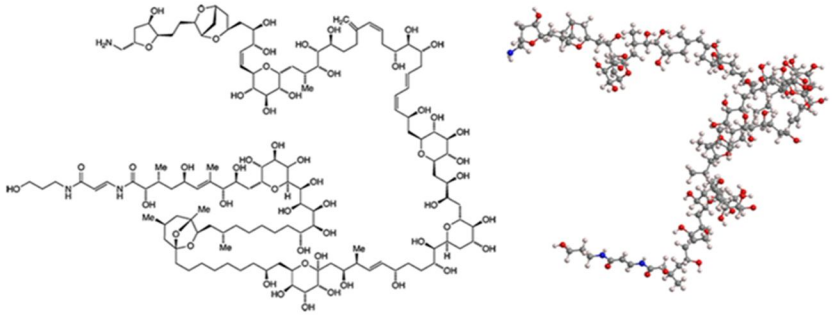
Palytoxin is a world's second deadliest poison produced by zoanthid corals of Palythoa Species and Zoanthus found in Pacific Ocean. It is a thermostable, non-proteinaceous, marine toxin with several analogs that causes lethality when ingested. Due to bioaccumulation of PTX compounds in sea food, Pescatarians are affected with several illnesses like metallic taste, fever, vomiting and finally death after ingestion.

Palytoxin analogs are almost similar properties and structure with changes at several positions forming different analogs. Toxicity differs in different animals and depends on the route of exposure and duration. As there is no standard technique to detect the compounds, no antidote or treatment is found.

Though few biological immunoassays are used to test the compounds and LC-MS/MS is used to confirm the presence of compounds in coral samples.

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II. CHEMICAL PROPERTIES



(a) (b)

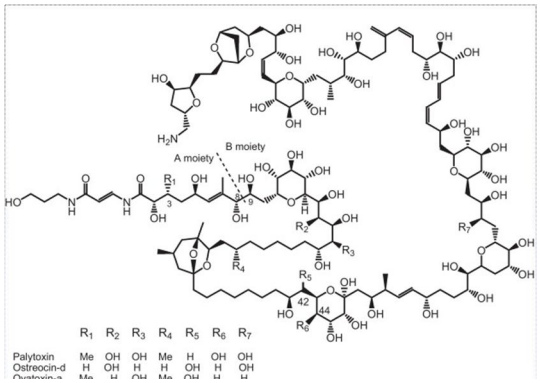
Fig 2 : Structure of Palytoxin (a) Molecular structure (b) 3D structure

Palytoxin is a thermostable, polyhydroxylated and partially unsaturated compound with 8 double bonds & long carbon chain. The molecular weights of PTX range from 2659 to 2680 Da. It is water-soluble and fat-soluble as it has 40 hydroxy groups, 64 chiral centers, and over 1021 alternative stereoisomers due to chirality and double bond cis-trans isomerism. It remains stable in aqueous solutions for prolonged periods while rapidly decomposes and loses its toxicity in acidic or alkaline medium.

A. Palytoxin & Analogs

It has multiple analogues with a similar structure like Ostreocin-D, Ovatoxin-a and several other Palytoxin Homologs. The Molecular weight of Ostreocin-D is 2635 Da while Ovatoxin is 2648 Da showing similar chemical properties & remarkable biological activity. Ostreocin-D and PTX shares same targets in the living individuals leading to Cytotoxicity and Hemolytic potency.

Palytoxin - $C_{129}H_{223}N_3O_{54}$, Ostreocin - $C_{127}H_{219}N_3O_{52}$,Ovatoxin - $C_{129}H_{223}N_3O_{52}$



a) Palytoxin structure showing positions where molecular groups change to form other analogs.



b) *Palythoa toxica*, a solitary polyp with disc shaped head found in the North direction island, Australia.

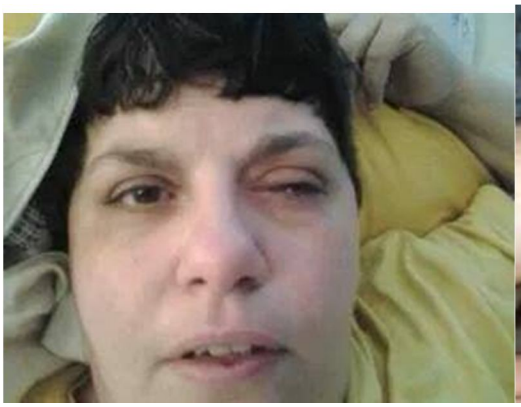


(c) Dinoflagellates of Ostreopsis genus found in the marine aquarium observed under light

Palytoxin analogs were first isolated from zoanthid Palythoa toxica and has been found in various members of a number of dinoflagellates of the Ostreopsis genus.

III. TOXICITY & SYMPTOMS IN MAMMALS

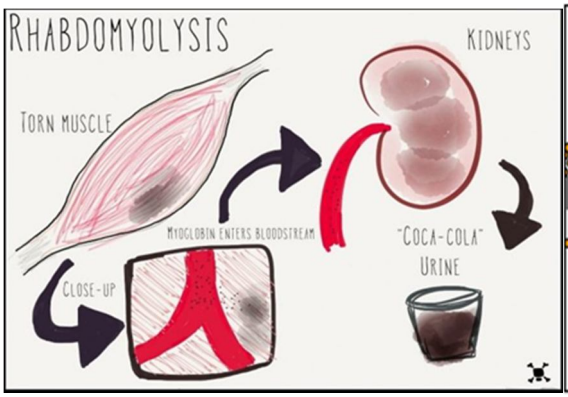
Toxicity in humans is due to consumption of sea food such as crab *Demania reynaudii* and sardine fish *Herklotsichthys quadrimaculatus* that are suspected to be contaminated or bioaccumulated with PTX that leads to clupeotoxism syndrome. Symptoms caused by Ovatoxin-a from aerosols include fever associated to bronchoconstriction, mild dyspnea and conjunctivitis was observed in some cases PTX is hemorrhagic to other mammals and has significant effects on Cardiovascular, Respiratory systems. PTX is recognized as potent tumor promoter and also caused non-lethal effects when applied to skin or eyes. In non-lethal cases the symptoms appeared in 6-8 hours after inhalation or dermal contact. In experimental records, through intravenous injection symptoms appeared in 30-60 minutes and after 4 hours of eye exposure in different animals. Dermal and Oral intoxication symptoms vary depending on the time of exposure.



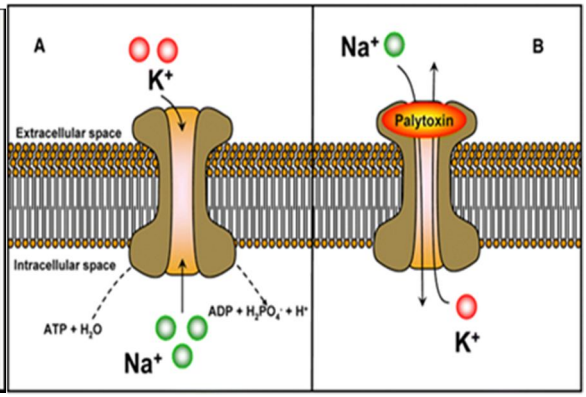
a) Case photo; a fish store worker eye affected after exposure to Palythoa corals.



b) Blisters formed on hands of aquarist due to dermal contact with PTX; after cleaning aquarium tank containing Palythoa corals.



c) Rhabdomyolysis showing torn muscle, kidney failure indicating color changed urine (coco cola urine)



d) Na^+/K^+ pump [Na^+/K^+ Atpase, a transmembrane protein] attached with palytoxin at Ouabain site leading to rapid diffusion of millions of ions per second

According to experimental toxicological data on PLTX & its analogs, toxin is highly lethal to animals by intraperitoneal or intravenous administration. On assessment of other routes of exposure, it is explained as PTX is extremely toxic after intramuscular or subcutaneous injection while no toxicity was found after intrarectal administration. The toxicity values obtained by IV route in rats is 0.089 and mice is 0.045 µg/kg while other mammals - dog, rabbit, guinea pig ranged between 0.025 & 0.45 µg/kg. The toxicity of PLTX in mammals is strongly dependent on the route of exposure.

Considering the lack of data on PLTX, an oral acute reference dose of 0.2 µg/kg has been established and toxicity in humans is estimated between 2.3 -31.5 µg through an intravenous (IV). Acute oral reference dose is suggested to be 64µg for a 60 kg individual.

IV. DETECTION

To detect PTXs in shellfish, cell-based assays such as cytotoxicity assays on neuroblastoma cells and hemolysis assays have also been developed but not standardized. PTX is detected and quantitatively measured by using the bio-assays but chemical techniques are needed to confirm the presence of Palytoxin in the samples. High-performance liquid mass spectrometry and LC-MS/MS methods are promising tools for PLTX detection. Using Ovatoxin and Ostreocin as reference compounds, analogs detected by LC/Q-TOF Mass Spectrometry, NMR. However, their optimization, validation, and the development of certified reference materials and standards are necessary.

V. CONCLUSION

Palytoxin and analogs are marine toxins found in soft corals of temperate regions of the Pacific Ocean, causing acute toxicity to Pescatarians after their consumption through edible marine organisms as they bioaccumulated. Adverse effects can also occur by inhalation, systemic exposures after contact with aerosolized seawater and during handling the corals containing aquaria. Poisoning cases have often indirectly imputed to PTXs based on symptoms, anamnesis, and environmental/epidemiological data. PTX is a highly potent toxin & also a novel skin tumor promoter that has been used in probing the role of different signaling mechanisms in Carcinogenesis and Palytoxin action can reveal new aspects of tumor promotion that can be used for anticancer purposes. Research Studies needed to be extensive bio technically as there are no antidotes or treatments to the toxic effects of PTX compounds. Palytoxin can be neutralized by soaking the coral in a $\geq$ 0.1% household bleach solution (1 part 5%-6 % Sodium Hypochlorite solution in 10 parts water) and also Activated Carbon has removed 99.7% of palytoxin in water.

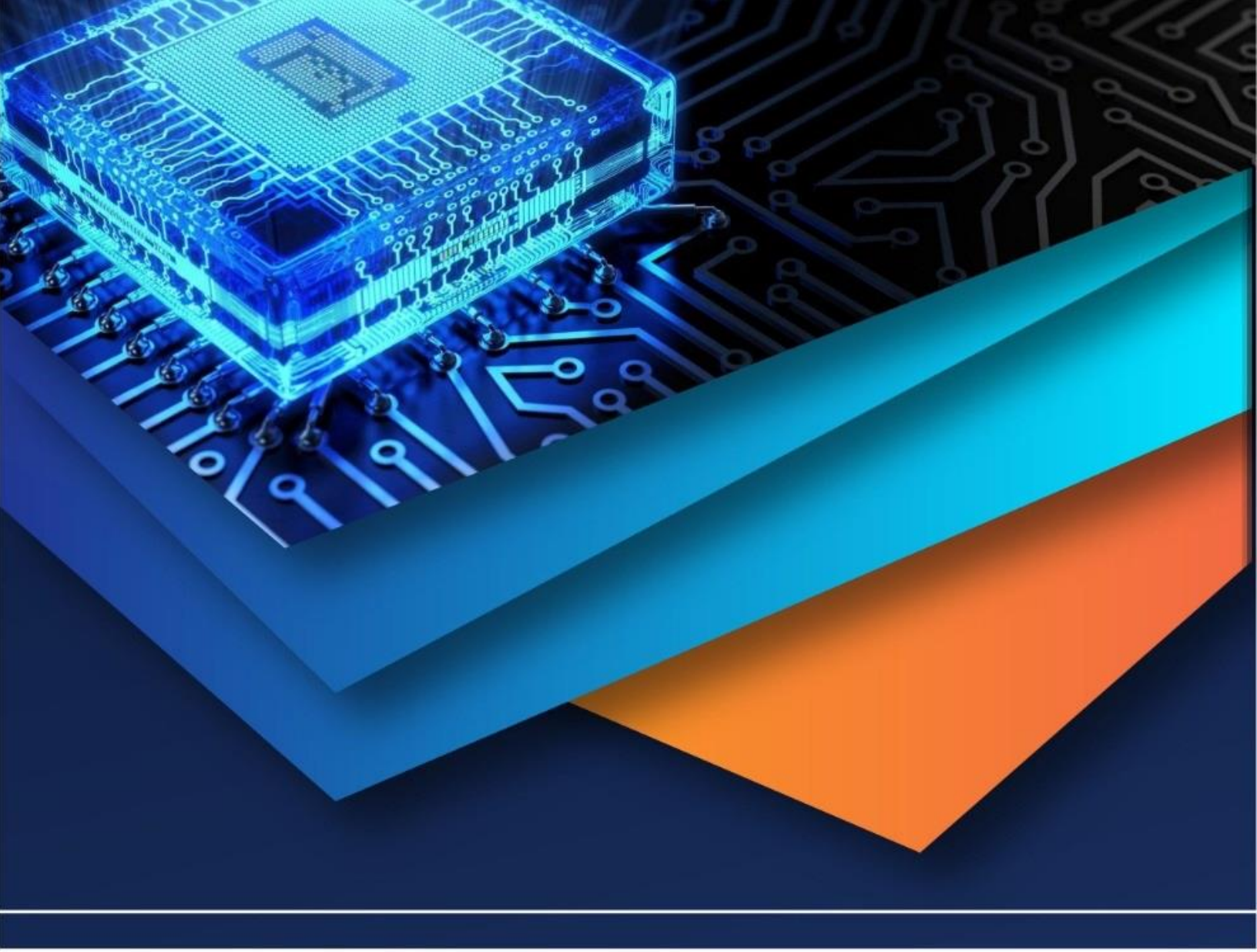
A. Case Studies

1) Suspected Palytoxin Inhalation Exposures in Aquarium Shops and Homes – Alaska.
2) Palytoxin Poisoning After Dermal Contact with Zoanthid Coral – Germany & USA.
3) Aquarium palytoxin induced keratoconjunctivitis – Canada.
4) Ingestion of Palytoxin caused fatal poisoning in Hawaii, Japan & Madagascar.
5) Palytoxin Analog-ovatoxin caused people fall ill – Italy.

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