CSIRO PUBLISHING The South Pacific Journal of Natural and Applied Sciences, **28**, 1-26, 2010
www.publish.csiro.au/journals/spjnas 10.1071/SP10001

Ciguatera fish poisoning and other seafood intoxication syndromes: A revisit and a review of the existing treatments employed in ciguatera fish poisoning

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Abstract

Ciguatera fish poisoning (CFP) is acquired through consumption of tropical reef fishes, contaminated with potent neurotoxins, ciguatoxins (CTXs), produced by benthic dinoflagellate of the Gambierdiscus genus. Both spatially and temporally unpredictable, a tainted fish is impossible to differentiate from an untainted one by appearance, taste, texture or odour. Given the predominance of reef fish in the diet of insular countries, the risk of CFP is ever-present. In the Pacific where the incidence of CFP is the highest, the consequences on public health and socio-economy can be extremely severe. Multidisciplinary in nature, the present review revisits the phenomenon of CFP, covering certain of its aspects, notably the etiology, toxicology, ecotoxicology, pharmacology, pathology and the treatments administrated. These aspects of CFP have been reviewed in relation to other poisoning syndromes: tetrodotoxin poisoning and other dinoflagellates- or diatoms-associated intoxications such as paralytic (PSP), diarrhetic (DSP), neurotoxic (NSP), amnesic (ASP) and azaspiracid shellfish poisoning (AZP) and palytoxin poisoning.

Based on case reports and bibliographic accounts, a list inventorying the western medicines prescribed to patients suffering from CFP has been established. Within the last two decades, several of the herbal remedies have been evaluated for their efficiencies in in vivo and in a number of in vitro tests, which have also been reviewed herein.

***Keywords**: Seafood poisoning, marine toxins, ciguatera fish poisoning (CFP), paralytic shellfish poisoning (PSP), diarrhetic shellfish poisoning (DSP), neurotoxin shellfish poisoning (NSP), amnesic shellfish poisoning (ASP), azaspiracid shellfish poisoning (AZP), tetrodotoxin (Fugu) poisoning, palytoxin poisoning, occidental medicine, traditional remedies*

1. Introduction

Mankind has always suffered from food-related poisoning. The accounts of one such intoxication, the ciguatera fish poisoning (CFP), also known as ciguatera, dates back to the beginning of the XVI century. Recorded in his writing, Pedro Martyr D'Anghera, a rapporteur working for the Spanish crown on board the ships of great explorers (Colombus, Cortez, Magellan and Vasco de Gama) attributed the cases of poisoning to intoxication by poisonous fish (Martyr d'Anghera, 1555; Bagnis, 1981; Lewis, 1986).

This fish-borne toxinological syndrome is prevalent in the tropical and subtropical areas, and is acquired through the consumption of marine fishes which have accumulated naturally occurring toxins through their diet. The origin of ciguatera is known to be benthic dinoflagellates belonging to the *Gambierdiscus* genus (Order Peridinales, Family Heteraulacaceae); the first species to be described being *Gambierdiscus toxicus* Adachi & Fukuyo (1979). These dinoflagellates are primarily found in sub-tropical and tropical areas (Gillespie *et al.*, 1986; Juranovic and Park, 1991; Laurent, 1993; Lehane and Lewis, 2000; de Fouw *et al.*, 2001; Lewis, 2001; 2006; Laurent *et al.*, 2005; Boydron-Le Garrec *et al.*, 2005a; Friedman *et al.*, 2008).

Although, consistently under-appreciated and under-reported (McKee *et al.*, 2001; Begier *et al.*, 2006), available evidence indicates that ciguatera is responsible for more than 50 000 cases of intoxication worldwide (Van Dolah, 2000a; Fleming *et al.*, 2006), and thus it represents the single largest cause of unpreventable fish poisoning (Isbister and Kiernan, 2005; Nicholson and Lewis, 2006).

1.1 Seafood Intoxication

Food is essential both for growth and for the maintenance of life. However, food can also be responsible for ill-health. Seafood-borne diseases are an emerging subset of food-borne illness, which have been on the increase since last few decades (Fleming and Eason, 1998; Fleming and Easom, 1998; Clemence and Guerrant, 2004). The recent epoch of international seafood trade expansion, development of the tourism industry, increasing anthropogenic stress on the marine environment, and the growing trend of utilization of a greater variety of marine organisms has been marked with increasing marine seafood-related disease incidences, a geographic spread of certain seafood illnesses and the emergence of new marine toxin diseases observed in human population (Bagnis *et al.*, 1970; Hallegraef, 2003; 2006; van Dolah, 2000a; Fleming *et al.*, 2001; 2006; Knap *et al.*, 2002).

An excellent source of high quality proteins, with low fat and high mineral content, the consumption of seafood has seen a steady rise over the recent decades to become an integral element of human diet globally (Pigott and Tucker, 1990; Soccol and Oetterer, 2003). Over 2.9 billion people worldwide rely on fish and fishery products for at least 15% of animal protein (FAO, 2009). To meet the growing global demand for seafood, the world seafood industry has expanded over last four decades to play a preeminent role in the economic and social well-being of several nations (Bell *et al.*, 2009; Pauly, 2009). In the island countries, particularly in the Pacific, seafood is a staple nutritive and sometimes the only economic resource (Dalzell, 1992; 1994; Dalzell and Adams, 1997). Since the 1970s, the marine catches in tropical waters of Pacific and the Indian

Oceans have shown a long-term gradual increase (FAO, 2009). Unfortunately, most cases of seafood poisoning caused by eating fish have been reported to originate from waters around tropical islands (Isblister and Kiernan, 2005).

Seafood intoxications are generally categorized as fish- or shellfish-associated, based on their primary transvectors, and are caused due to the presence of biological (bacterial spoilage related to improper handling or by contamination with viruses or parasites) or chemical (contamination *via* chemical toxins through anthropogenic activities or *via* biotoxins issued from micro-organisms like diatoms, cyanobacteria and dinoflagellates) hazards (Huss *et al.*, 2000; Fleming *et al.*, 2001; 2006; Knap *et al.*, 2002). Though a natural phenomenon, harmful algal blooms (HABs) seem to have become more frequent, more intense and more widespread. Some of the contributing factors attributed to such observations include a greater scientific awareness and better surveillance systems The local, regional or global favorable conditions of growth and transportation of algal cyst *via* ship ballast water transport or shellfish transplantation are also believed to contribute to the expansion of seafood intoxication (van Dolah, 2000a; Hallegraef, 2003; 2006).

Marine biotoxins are among the most potent naturally occurring toxins known to date (Wang, 2008). They are responsible for extensive fish and shellfish die-offs and have been implicated in the episodic mortalities of marine mammals, birds and other animals at the top of marine food web (Geraci *et al.*, 1989; Burkholder *et al.*, 1992; Scholin *et al.*, 2000; Jessup *et al.*, 2009; Landsberg *et al.*, 2009; de la Riva *et al.*, 2009). Worldwide, these toxin-producing marine microorganisms cause more than 60 000 poisoning events annually with an associated mortality rate of 1.5% (van Dolah, 2000a). Of these, human diseases associated with exposure to dinoflagellate biotoxins occupy the principal position (Knap *et al.*, 2002; Camacho *et al.*, 2007).

1.2 Dinoflagellate-Associated Toxicoses

The dinoflagellates are important components of phytoplankton that provide vital nutrition support to filter-feeding bivalve shellfish and to the larvae of crustaceans and finfish, many of which are commercially important (Hallegraef, 2003; Camacho *et al.*, 2007). Of the 3400-5000 species of extant marine phytoplanktons, about 300 can proliferate in high numbers (Barber and Diaz, 2003; Hallegraef, 2003). A certain 80-90 of these species are known to have the capacity of producing phycotoxins (van Dolah, 2000a; Hallegraef, 2003; Camacho *et al.*, 2007). Of these, 70 are dinoflagellates which make them the largest group of harmful species that impact humans (Camacho *et al.*, 2007). Though mass proliferations of pelagic dinoflagellates are known to take part in HABs, several benthic species are also known to produce highly potent poisons.

The possible presence of natural toxins in fish and shellfish has been known since antiquity. However, it has been only in the past few decades, in view of current world food priorities, that extensive studies have been devoted to the toxicology and pharmacology of marine seafood poisonings. As a result, four major seafood poisoning syndromes (van Dolah, 2000b; Barbier and Diaz, 2003; Zaccaroni and Scaravelli, 2008) have been identified from the dinoflagellate toxins: paralytic shellfish poisoning (PSP), diarrhetic shellfish poisoning (DSP), neurotoxin shellfish poisoning (NSP) and ciguatera fish poisoning (CFP).

Besides these, there are emerging reports of several new poisoning syndromes (Wang, 2008) resulting from newly appearing dinoflagellate toxins such as azaspiracid shellfish poisoning (AZP) and palytoxin (Table 1-3). Other well-described intoxications include amnesic shellfish poisoning (ASP) and tetrodotoxin poisoning from toxins issued from diatoms and from unknown sources, respectively (Table 1-3).

These various toxic syndromes have contributed to an increase in global public concerns on the importance of marine biotoxicants, especially those associated with dinoflagellates and have been subject of many excellent reviews (Mons *et al.*, 1998; Bricelj and Shumway, 1998; van Apeldoorn *et al.*, 1999; van Apeldoorn *et al.*, 2001; de Fouw *et al.*, 2001; Friedman *et al.*, 2008; Katikou, 2008; McNabb, 2008; Munday, 2008; Pulido, 2008; Ryan *et al.*, 2008; Tubaro *et al.*, 2008; Twiner *et al.*, 2008; Vale, 2008; Watkins *et al.*, 2008).

1.3 Fish -Borne Poisonings

Thousands of marine organisms have been listed as poisonous or venomous, some of which cause discomfort, illness or even death in man (Halstead, 1959; 2001a; 2001b). However, in terms of incidence, given its popularity (Whittle and Gallacher, 2000), the most recurrent forms of marine poisoning arise from consumption of fish, and particularly so in tropical and subtropical insular regions (Lehane and Lewis, 2000; Pearn, 2001; Barnett and DiPalma, 2004; Huss *et al.*, 2004; Isblister and Kiernan, 2005; Barceloux *et al.*, 2008). The intoxication, resulting after one has been in contact or ingested a poisonous vertebrate fish, is categorized under *ichthyotoxism*.

Derived from Greek, the prefix *ichthyo* signifies pertaining to fishes, while *toxism* denotes poisoning. This denomination includes various piscine toxicities (Bagnis *et al.*, 1970; Halstead, 2001a; Zaccaroni and Scaravelli, 2008), which are classed according to the distribution of ichthyotoxins in the biological compartments of the fish (Table 4).

Ichtyosarcotoxism, by far the most common form in terms of incidence, encompasses different types of intoxications which have been further delineated either on the basis of the species of causative fish or of the clinical picture produced (Table 5). The clinical manifestations of ichthyosarcotoxism are routinely characterized by sensory disturbances. Though lacking precise definition, due to the diversity in the fish species and in the nature of toxins implicated, there appears to be broad differentiation between characteristic illnesses which appear following ingestion of diverse species of toxic fish and illnesses which occur following ingestion of particular species (SPC, 1968).

Thus categorized according to the taxonomy, the ichthyosarcotoxism groups include elasmobranch poisoning from ingestion of sharks, skates and rays, clupeoid poisoning from ingestion of sardines and herrings, scombroid poisoning from ingestion of tuna, mackerel,

Table 1. Human intoxication syndromes caused by marine biotoxins, toxins implicated, causative agents, vectors and geographical distribution (Baden *et al.*, 1995; Knap *et al.*, 2002; Backer *et al.*, 2003; Hallegraef, 2003; Huss *et al.*, 2004).

Disease	**Causative Organism(s)**	**Toxin(s) Implicated**	**Vectors (Known and Potential)**	**Geographical Distribution**	**First Recorded Incidence**
Paralytic shellfish poisoning (PSP)	Red tide dinoflagellate species: *Alexandrium*, *Gymnodinium catenatum*, *Pyrodinium bahamense*, *Gonyaulax*	Saxitoxins (STXs), gonyautoxins (GTXs), N-sulfocarbamoyl analogs	Clams, mussels, oysters, gastropods, cockles, fish, scallops, whelks, lobsters, copepods, crabs	Temperate to tropical worldwide	1927
Diarrhetic shellfish poisoning (DSP)	Red tide dinoflagellate species: *Dinophysis*, *Prorocentrum*, *Coolia*, *Protoperidinium oceanicum*, *Phalacroma rotundatum* *Protoceratium reticulatum*, *Lingulodinium polyedrum*, *Gonyaulax spinifera*	Okadaic acid (OA), dinophysistoxins (DTXs), pectenotoxins (PTXs) yessotoxins (YTXs)	Mussels, scallops, clams, gastropods	Temperate worldwide	1961
Amnesic shellfish poisoning (ASP)	Red tide diatom species: *Pseudo-nitzschia*	Domoic acid	Mussels, anchovies crabs,	Canada, NW, USA, Ireland	1987
Neurotoxic shellfish poisoning (NSP)	Red tide dinoflagellates species: *Karenia*, *Chatonella*, *Karenia brevis* (formerly *Gymnodinium breve* and *Ptychodiscus brevis*), *Fibrocapsa japonica*, *Heterosigma akashiwo*,	Brevetoxins (PbTxs)	Oysters, clams, mussels, cockles, whelks, fish	Gulf of Mexico, North Carolina, Japan, NZ	1844
Ciguatera fish poisoning (CFP)	Epibenthic dinoflagellates species: *Gambierdiscus*	Ciguatoxins (CTXs), scaritoxin, maitotoxins (MTXs), palytoxin, gambierol	>400 coral reef fish, snail, shrimps, crabs	Subtropical to tropical worldwide	1500s
Tetrodotoxin (Fugu) poisoning	Bacteria species: *Vibrio pelagius*, *Alteromonas tetraodonis*, *Shewanella alga*?	Tetrodotoxin (TTX)	>40 Pufferfish, porcupine fish, sun fish, toadfish, trumpet shell, horseshoe crab, xanthid crabs, starfish, octopus, marine worms	Japan, China, Mexico	2800 BC
Azaspiracid shellfish poisoning (AZP)	Red tide-associated dinoflagellates *Protoperidinium crassipesb*	Azaspiracids (AZAs)	Mussels, oysters, scallops, clams, crabs	Europe	1995
Palytoxin poisoning	Epibenthic dinoflagellates *Ostreopsis* sp.	Palytoxin (PLX) and ostreocins	Crabs, sea urchins, mackerel, triggerfish, sardines, fish	Europe, Phillipines, Brazil, Japan	1987

? - Not confirmed.

Table 2. Human intoxication syndromes caused by marine biotoxins, mode of action and chemistry (van Dolah, 2000a,b; Knap *et al.*, 2002; Backer *et al.*, 2003; Katikou, 2008; Ojeda *et al.*, 2008; Paz *et al.*, 2008; Suzuki, 2008; Twiner *et al.*, 2008; Wang, 2008).

Toxin	Congeners	Disease	Principle Action Target	Chemical Backbone	Nature
Saxitoxins (STXs)	>24	Paralytic shellfish poisoning (PSP)	Site 1 Na^+ channel blocker	Tetrahydropurine	Hydrophilic
Gonyautoxins (GTXs)			Site 1 Na^+ channel blocker	Tetrahydropurine	Hydrophilic
N-sulfocarbamoyl derivatives			Site 1 Na^+ channel blocker	Tetrahydropurine	Hydrophilic
Okadaic acid (OA)	>6	Diarrhetic shellfish poisoning (DSP)	Phosphatase inhibitor	Polyether	Hydrophilic
Dinophysistoxins (DTXs)			Phosphatase inhibitor	Polyether	Hydrophilic
Pectenotoxins (PTXs)	>15		ND	Polyether	Lipophilic
Yessotoxins (YTX)	36		ND	Polyether	Lipophilic
Domoic acid (DA)	17	Amnesic shellfish poisoning (ASP)	Glutamate receptor agonist	Tricarboxylic amino acid	Hydrophilic
Brevetoxins (PbTxs)	>10	Neurotoxic shellfish poisoning (NSP)	Site 5 Na^+ channel activator	Polyether	Lipophilic
Ciguatoxins (CTXs), scaritoxin	>20	Ciguatera fish poisoning (CFP)	Site 5 Na^+ channel activator	Polyether	Lipophilic
Maitotoxins (MTXs)	3		Ca^{2+} channel activator	Polyether	Hydrophilic
Palytoxin	8		Na^+-K^+ ATPase inhibitor	Polyether	Lipophilic and hydrophilic
Gambierol	1		K^+ channel blocker	Polyether	Lipophilic
Tetrodotoxin (TTX)	>3	Tetrodotoxin (Fugu) poisoning	Site 1 Na^+ channel blocker	Densely functionalized cyclohexane ring with a cyclic guanidine moiety	Hydrophilic
Azaspiracids (AZAs)	>20	Azaspiracid shellfish poisoning (AZP)	ND	Polyether	Lipophilic
Palytoxin	8	Palytoxin poisoning	Na^+-K^+ ATPase inhibitor	Polyether	Lipophilic and hydrophilic

ND - Not determined.

Table 3. Human intoxication syndromes caused by marine biotoxins, symptoms, prevention and treatment (Baden *et al.*, 1995; Knap *et al.*, 2002; Backer *et al.*, 2003; Hallegraef, 2003; Huss *et al.*, 2004; Isbister and Kiernan, 2005).

Disease	Prevention	Onset	Duration	Acute Symptom	Chronic Symptom	Treatment
Paralytic shellfish poisoning (PSP)	No antitoxin, avoid potentially toxic shellfish especially just after HABs, detection of toxin and closure of shellfish beds	0.5-2 h	Days	Primarily neurologic: descending paresthesia, muscular non-coordination, muscular paralysis, respiratory failure and death	None observed	Supportive
Diarrhetic shellfish poisoning (DSP)	No antitoxin, avoid potentially toxic shellfish especially just after HABs, detection of toxin and closure of shellfish beds	0.5- 3 h	Days	Entirely gastrointestinal: diarrhea*****, nausea, vomiting, abdominal pain	None observed	Supportive
Amnesic shellfish poisoning (ASP)	No antitoxin, avoid potentially toxic shellfish, detection of toxin and closure of shellfish beds	<24 h	Years	Gastrointestinal and neurologic: amnesia*****, coma and death	Amnesia	Supportive
Neurotoxic shellfish poisoning (NSP)	No antitoxin, avoid potentially toxic shellfish especially just after HABs, detection of toxin and closure of shellfish beds	0.5-3 h	Days	Neuromuscular and mild gastrointestinal: muscular pain, paresthesia, reversal of temperature sensation*****and hypotension*****	None observed	Supportive
Ciguatera fish poisoning (CFP)	Difficult, no commercially available detection methods, no antitoxin available, either avoid large predacious coral reef fish or eating the viscera of fish	5-24 h	Years	Gastrointestinal, neurological and cardiovascular: nausea, diarrhea, reversal of temperature sensation*****, tachycardia, bradycardia	Paresthesia	Symptomatic and supportive: *i.v.* rehydration, antiemetics, antidiarrhoeal, atropine, anti-depressants, *i.v.* D-mannitol
Tetrodotoxin (Fugu) poisoning	Avoid inherently toxic fish species or have the fish specially prepared	5-30 min	Days	Acute descending paresthesia***** and minor gastroenteritis that can lead to, muscular paralysis, cardiac dysfunction, respiratory paralysis***** and death	None observed	Supportive: gastric lavage with sodium bicarbonate, activated charcoal, endotracheal intubation
Azaspiracid shellfish poisoning (AZP)	No antitoxin, avoid potentially toxic shellfish, detection of toxin and closure of shellfish beds	3-18 h	Days	Severe gastroenteritis	None observed	NR
Palytoxin poisoning	No antitoxin, may be distinguished by an unusual taste imparted to the fish	NR	NR	Gastrointestinal, neurological, and autonomic: respiratory distress and death	NR	NR

NR - Not reported.
*Generally accepted as pathognomonic signs of the intoxication syndrome.

Table 4. Classification of fish-borne intoxications according to the type and the origin of the toxic compounds (adapted from Bagnis *et al.*, 1970).

Class	Biological Compartment	Fish Species Implicated
Ichthyohemotoxism	Injection, absorption or ingestion of fresh fish blood	Anguillidae, Congridae, Muraenidae and Ophichthidae
Ichthyohepatotoxism	Fish liver that probably contains excessive amounts of vitamin A	Scombridae, Serranidae, Sparidae and Trichodontidae
Ichthyootoxism	Eggs and gonads of mainly freshwater and a few marine fish species	Barbus, Schizothorax, Tinca and Stichaeus
Ichthyoalleinotoxism "hallucinogenic fish poisoning"	Upon ingestion of head or flesh of certain of reef fishes in the tropical Pacific and Indian oceans	ND
Ichthyoacanotoxism	From injuries sustained from stings, spines or teeth of venomous fish poisons that are secreted from venom apparatus	ND
Ichthyocrinotoxism	Venoms are produced by means of glandular structure, often in the skin, independent of a true venom apparatus	Myxinidae, Grammistes, Rypticus and Ostraciidae
Ichthyosarcotoxism	Upon ingestion of flesh and other parts of the fish	Numerous coral reef-dwelling fishes

ND - Not determined.

Table 5. Classification and general characteristics of different types of ichtyosarcotoxism apart from ciguatera fish and tetrodotoxin poisonings (adapted from Bagnis *et al.*, 1970; Zaccaroni and Scaravelli, 2008).

Name	Species	Clinical Characteristics	Toxin
Clupeotoxism	Herrings, anchovies, sardines, tarpons, bonefishes, deep-sea bonefishes	Short incubation time digestive syndrome, pruritus, tachycardia, vertigos, cyanosis. Coma and death are not so rare	Palitoxin? Mixed toxins?
Hallucinatory Fish Poisoning	Sea chubs, mullets, goatfish, surmullets	Short incubation time Gastrointestinal and psychological disturbances, hallucination, vertigos, behavior alterations, motor incoordination	Various, unknown toxins
Carchatoxisms	Various sharks species	Both nervous and digestive signs	Mixed toxins Carchatoxins
Scombroidotoxism	Scombridae, tuna, bonitos, mackerel	Short incubation time Rapid evolution, nervous and digestive signs, regression within 8-12 h	Histamine and biogenic amines
Cyclostome Poisoning	Lampreys, hagfish	Nausea, vomiting, dysenteric diarrhea, tenesmus, abdominal pain and weakness	ND
Gempylotoxic Fish	*Gempylidae* (castor oil fish)	Diarrhea	Oil comprised mainly of oleic acid
Elasmobranch Poisoning	Sharks, skates, rays	Gastrointestinal, neurological and cardiovascular symptoms	ND
Chimaera Poisoning	Ratfishes	NR	ND

? - Assumed but not confirmed.
NR - Not reported.
ND - Not determined.

bonito, skipjack and mahi-mahi (Table 5), and tetrodotoxin poisoning from ingestion of flesh, viscera or skin of puffers and puffer-like fish (Table 1-3). Ichthyosarcotoxism resulting from ingestion of diverse species of toxic fish includes the hallucinatory poisoning (Table 5) and CFP (Table 1-3), and are primarily diagnosed based on clinical manifestations (SPC, 1968; Bagnis *et al.*, 1970; Halstead, 2001a; Zaccaroni and Scaravelli, 2008).

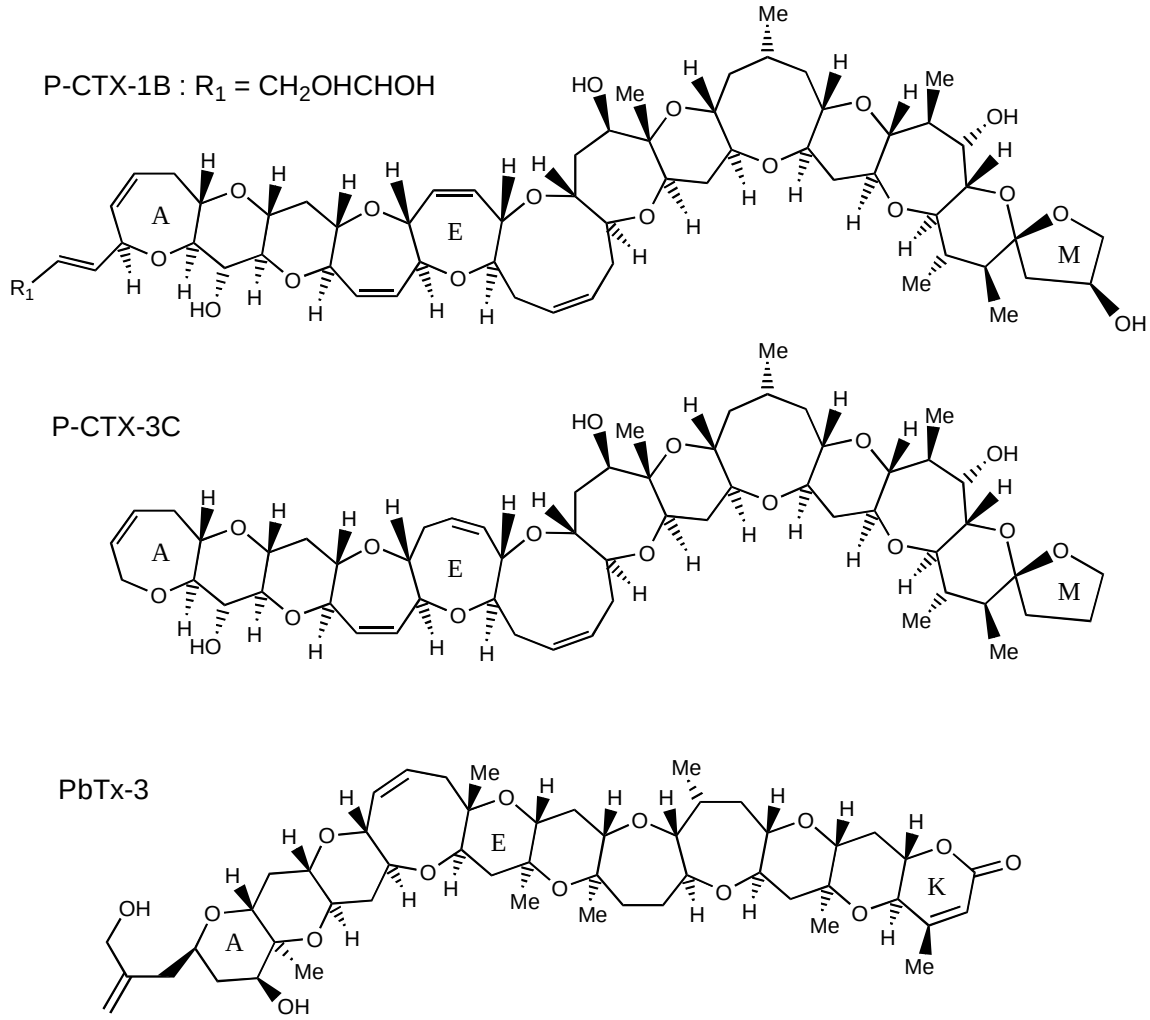

Figure 1. Chemical structure of some polyether marine neurotoxins (P-CTXs : Pacific ciguatoxins; PbTxs : brevetoxins).

2. Ciguatera Fish Poisoning

An unpreventable form of ichthyosarcotoxism, CFP is caused after consumption of tropical marine fish species that seem without risk but are tainted with one or more naturally occurring neurotoxins from the family of ciguatoxins (CTXs). The disease, commonly afflicting the regions of Pacific and Indian Ocean and the Caribbean Sea, is both spatially and temporally unpredictable and impossible to detect by appearance, taste, texture or odor of fish caught (Lehane and Lewis, 2000; Lewis *et al.*, 2000; Lewis, 2001; Laurent *et al.*, 2005; Lewis, 2006; Friedman *et al.*, 2008). More than 400 species of near-shore tropical fishes, ranging over a broad phylogenetic spectrum, have been incriminated as potential vectors of this intoxication (Halstead, 1978). Despite the fact that this marine toxin illness is very often under-diagnosed and under-reported, it is nonetheless, the most common non-bacterial intoxication, estimated to between 50 000 to 100 000 cases per year (McKee *et al.*, 2001; Begier *et al.*, 2006; Fleming *et al.*, 2006).

2.1 Toxins Source

The term ciguatera was coined in 1866 by a Cuban doctor Felipe Poey, after the vernacular name of a marine gastropod, *Turbo* (syn. *Livona*) *pica*, responsible for intoxications in Cuba (Poey, 1866). Despite the long history, it was only three decades ago, that the scientists gained insight into the etiology of CFP. An exceedingly thorough examination of the feeding behavior of ciguatoxic fish in the Pacific by Randall (1958) led to the theory of food chain whereby the toxin was presumed to be produced by an unspecified benthic microorganism, which is first ingested by herbivorous fishes and then transferred to larger carnivores. Supposing the causative agent might be an alga, a fungus, a protozoan or a bacterium, Randall (1958), on the basis of circumstantial evidence, favored an unidentified benthic cyanobacterium as the likely precursors of the toxins. A good part of this theory proved to be remarkably accurate, although nearly 20 years passed before its validity was proven by the identification of the source organisms.

The breakthrough occurred when Yasumoto *et al.* (1977a; 1977b) found considerable toxicity in a sample of algae and detritus collected from the surface of dead coral in the Gambier Islands of French Polynesia during an epidemic of ciguatera in 1976 that correlated with the stomach contents of fishes. The microalga in question was a benthic dinoflagellate. Tentatively identified as *Diplopsalis* sp. (Yasumoto *et al.*, 1977b), it was later placed under a new genus and named *G. toxicus* (Adachi and Fuyuko, 1979).

Since this first milestone, four other species in this

genera, *G. belizeanus* sp. nov. (Faust, 1995), *G. yasumotoi* sp. nov. (Holmes, 1998), *G. australes*, *G. pacificus* and *G. polynesiensis* (Chinain *et al.*, 1999; 2009) have been described. Though, the four latter species have been reported to be toxic in culture (Holmes, 1998; Chinain *et al.*, 1999), their implication in CFP remains to be demonstrated. On the other hand, the toxicity of *G. belizeanus* is yet to be determined. In addition, in many ciguatera-endemic regions, the co-occurrence of other toxic benthic dinoflagellates belonging to the genera *Ostreopsis*, *Coolia* and *Prorocentrum* with the *Gambierdiscus spp.* has lead to the presumption of their role as source of toxins in the ciguatera food-chain (Backer *et al.*, 2003).

The origin of the toxins that cause CFP in the Caribbean Sea (Poli *et al.*, 1997; Vernoux and Lewis, 1997; Lewis *et al.*, 1998; Pottier *et al.*, 2002) and Indian Ocean (Hamilton *et al.*, 2002a; 2002b) has yet to be determined (Lewis, 2001; 2006). Recently, benthic cyanobacteria have also been suspected in this phenomenon (Hahn and Capra, 1992; Endean *et al.*, 1993; Laurent *et al.*, 2008; Kerbrat *et al.*, 2009). In New Caledonia, some recently reported cases of ciguatoxicosis have resulted after a meal of giant clams, which has led the authors to suggest the name, ciguatera shellfish poisoning (Laurent, personal communication).

2.2 Toxins Implicated

Ciguatoxins (CTXs) are the neurotoxins that are predominantly responsible for CFP. Other toxins isolated from *G. toxicus*, *Ostreopsis* spp., *Coolia* spp. and *Prorocentrum* spp., namely the maitotoxins (MTXs), okadaic acid (OA) and palytoxin (PTX), have also been implicated in CFP (Anderson and Lobel, 1987; Holmes and Lewis, 1994; Lewis, 2001; 2006). Though, theimplication of these different toxins in CFP could in the least explain the complex medical symptoms they produce in human consumers, it still needs to be formally demonstrated.

The CTXs form a family of chemical compounds, closely related in structures with a molecular weight of 941-1141 Da (Lewis, 2006). These potent toxins consist of highly oxygenated long chain alkyl compounds, in which most of the oxygen atoms occur as cyclic ether linkage that form 13-14 rings, which are fused into a mostly rigid, ladder-like structure. (Figure 1). Heat-resistant, fat-soluble, CTXs are polyheterocyclic toxins possessing structural framework reminiscent to that of the brevetoxins (PbTxs) (Figure 1). The PbTxs belong to another family of potent lipid-soluble polyether toxins that are produced by the red-tide forming marine dinoflagellate *Karenia brevis* (formerly *Ptychodiscus brevis* then *Gymnodinium breve*) which is implicated in NSP intoxications (Table 1-3) (Baden, 1989; Dechraoui *et al.*, 1999; Watkins *et al.*, 2008).

Originally isolated in 1967 in a partially pure form from specimens of Javanese giant moray eels *Gymnothorax javanicus* (Scheuer *et al.*, 1967), the structural formula of the first CTX was first elucidated in 1989 on the basis of 350 µg of poison obtained from 4 tons of *G. javanicus* (Legrand *et al.*, 1989; Murata *et al.*, 1989; Yasumoto, 2005). At present, three classes of CTXs are recognized and the prefixes P-, C- and I- signifying "Pacific ocean", "Caribbean sea" and "Indian ocean" are denominated to distinguish the CTXs based on their geographic origin (Murata *et al.*, 1989; 1990; Lewis *et al.*, 1991; Satake *et al.*, 1993; 1997; 1998; Vernoux and Lewis, 1997; Hamilton *et al.*, 2002a; 2002b). This being, for certain CTXs of the Pacific that were isolated prior to C-CTXs and I-CTXs, this prefixion is not used.

As a consequence, the first CTX to be purified and structurally elucidated was called CTX-1 but is now also known as CTX-1B or P-CTX-1. To date, more than 23 structures of CTX congeners have been resolved (Yasumoto *et al.*, 2000; 2005; Dickey, 2008). All origins confounded, geographical and biological, in 2002, the analogues of CTXs tallied to 39; more precisely, 23 P-CTXs, 12 C-CTXs and 4 I-CTXs (Boydron-Le Garrec *et al.*, 2005a). This includes those isolated from fish, both herbivores and carnivores, and from dinoflagellates, in wild and cultured. The CTXs isolated from extracts of dinoflagellates are generally grouped under the name "gambiertoxins" (GTXs).

2.3 Ecotoxicology of Ciguatoxins

Ciguatera fish poisoning is a complex ecotoxicological phenomenon that constitutes a serious threat to the development of industry of seafood fisheries and international tourism of sub-tropical and tropical island communities (Lewis, 1979; Olsen, 1988; Lewis, 1992; Bagnis, 1992; Lewis and Ruff, 1993; Glaziou and Legrand, 1994; Epstein and Rapportt, 1996; Laurent *et al.*, 2005). As Randall (1958) foresaw, the odyssey of the incriminated toxins from the *G. toxicus* cells to the human consumer involves the food link.

This benthic dinoflagellate will frequently grow as an epiphyte on macroalgae colonizing the dead corals or other surfaces. Consequently, it is not part of the plankton community and hence takes no part in the appearance of red-tides. Where toxicity is an exception in planktonic dinoflagellates, in the benthic species like *Gambierdiscus* it is rather a norm (Anderson and Lobel, 1987). The prevalence of potent toxins among these dinoflagellates is believed to provide a competitive advantage over co-occurring microalgal species.

The CTXs and/or their precursors are introduced into the marine food web *via* the herbivorous fishes grazing on coral or macroalgae harboring the dinoflagellates *G. toxicus*, which in turn once preyed on is transferred to carnivorous fishes and so on until they reach the human consumers who are the final link of the food chain (Helfrich and Banner, 1963, Banner, 1974; Bagnis *et al.*, 1980; Juranovic and Park, 1991; Lewis and Holmes, 1993; Lewis *et al.*, 1994; Lewis, 2001). As the toxins are passed up the trophic chain, they tend to concentrate or bio-accumulate (Johnson and Jong, 1983; Gillespie *et al.*, 1986). As the result of this process, the predators at the end of the food web harbor the highest concentrations of toxins. Large carnivorous fishes like, barracuda, snapper, grouper, jacks and moray eel are particularly notorious for causing severe CFP, arising from their capacity to have accumulated high toxins loads through their diet (Kuberski, 1979; van Dolah, 2000a; Pearn, 2001).

The resembling chemical structures of these toxins put in relation to the organisms from which they were issued indicates that the toxins found in fish flesh are more

oxygenated and thus are more polar than the congeners isolated from *G. toxicus* (Legrand *et al.*, 1992). It is believed that the fish metabolites, P-CTX-1B, -2, and -3 (Lewis *et al.*, 1991) are derived from oxidation of the parent gambiertoxins CTX-4A and CTX-4B produced by *Gambierdiscus* spp. from the Pacific region (Murata *et al.*, 1989; 1990; Lewis and Holmes, 1993; Yasumoto and Murata, 1993). This oxidative conversion reminds us of the role of the cytochrome (P450), a family of 60 enzymes involved in the first step of the detoxification process in the liver. The lipophilic toxins, like aflatoxin are detoxified by these enzymes through oxidative biochemical reactions to hydrophilic metabolites, which are then eliminated into urine. Thus the oxidation of P-CTX-4B to P-CTX-1 could be regarded as a kind of detoxification process. But what actually happens is the opposite of detoxification, as the toxicity of CTXs increases with the oxidation. The toxicity of P-CTX-1 is in fact nine-fold superior than that of CTX-4B (Yasumoto, 1993). This process of toxification is known as bio-transformation.

2.4 Clinical Manifestations

The clinical presentation of CFP (Table 6) has been addressed in substantial detail by various authors around the world (Bagnis *et al.*, 1979; Gillespie *et al.*, 1986; Geller *et al.*, 1991; Katz *et al.*, 1993; Ruff and Lewis, 1994; de Haro *et al.*, 1997; 2003; Lehane and Lewis, 2000; Ng and Gregory, 2000; Farstad and Chow, 2001; Goodman *et al.*, 2003; Arena *et al.*, 2004; Cheng and Chung, 2004; Laurent *et al.*, 2005; Kipping *et al.*, 2006; Nicholson and Lewis, 2006; Dickey, 2008; Friedman *et al.*, 2008). Globally more than 175 acute and chronic gastrointestinal, neurological and/or generalized disturbances, and to a lesser extent, cardiovascular symptoms have been described (Wang, 2008). The symptoms of ciguatera vary in different oceans, attributable to regional (P-, C- and I-) suite of toxins. In the Pacific Ocean neurological symptoms predominate, while in the Caribbean Sea the gastrointestinal symptoms are dominant features. The toxins from Indian Ocean give rise to symptoms that are typical of CFP in the Pacific, in addition to neuropsychiatric alterations (Lehane and Lewis, 2000; Lewis, 2001; 2006; Friedman *et al.*, 2008). However, the nature, duration, and the severity of symptoms can also vary after a meal of fish captured within a restricted location. This is likely to stem from individual susceptibility, and from the quantity and type of CTXs consumed, influenced by the part (head, liver, viscera, or flesh) and type (herbivorous, carnivorous) of fish consumed (Glaziou and Martin, 1993; Lewis *et al.*, 2000; de Fouw *et al.*, 2001; Lewis, 2001).

Nevertheless, in its typical form, CFP announces with an acute but prodromal gastroenteritis, after which the chronic neurological symptoms comprising of neurocutaneous and musculoskeletal features progressively set in. The cardiovascular disorders generally also occur in the prodromal period but are more sustained than gastrointestinal symptoms. While the acute illness generally abates within a few days to a week, the neurological symptoms involving the peripheral sensory and motor systems can persevere for months and even years (Table 6) (Morris *et al.*, 1982a; 1982b; Gillespie *et al.*, 1986; Lange *et al.*, 1992; Butera *et al.*, 2000; Ting and Brown, 2001; Farstad and Chow, 2001; Isbister and Kiernan, 2005; Friedman *et al.*, 2008).The enduring neurological feature of CFP, that sets it apart from other seafood intoxications, is commonly associated with signs of polyneuropathy (Sozzi *et al.*, 1988; Deroiche *et al.*, 2000; Schnorf *et al.*, 2002; Isbister and Kiernan, 2005; Chateau-Degat *et al.*, 2007a,b). The persistent neurological pain and dysfunction lasting months to years associated with chronic CFP has been reported to yield a symptom presentation similar to chronic fatigue syndrome (Pearn, 1996; 1997; 2001; Racciatti *et al.*, 2001). The reversal of temperature discrimination or cold allodynia, also known as paradoxical dysesthesia, is considered as the telltale sign of CFP. However, it is not always present (Bagnis *et al.*, 1979; Johnson and Jong, 1983; Lewis *et al.*, 1993; Perkins and Morgan, 2004; Isbister and Kiernan, 2005) and is also documented in severe cases of NSP (Knap *et al.*, 2002; Cuypers *et al.*, 2007; Friedman *et al.*, 2008) (Table 3).

Frequently observed in persons who have ingested larger predatory fish, the cardiac signs are indicative of severity of the disease and can be life-threatening (Kodama and Hokama, 1989; Chan and Wang, 1993; Lehane and Lewis, 2000). In such cases, default of proper diagnostic and medical care, death can occur due to dehydration, cardiovascular shock, cardiac arrhythmias or respiratory failure (Bagnis *et al.*, 1979; Bavastrelli *et al.*, 2000; Lehane and Lewis, 2000; Wasay *et al.*, 2008). Most fatal cases were reported when the head, gonads, roe or other internal organs were consumed (Lehane and Lewis, 2000). Due to its lipid solubility, CTXs tend to concentrate in these body parts. The fatality due to CFP is estimated to under 0.1% (Swift and Swift, 1993). Nevertheless, the length of altered neurosensory (paresthesia in the extremities, myalgia, arthralgia and pruritus) and neuropsychiatric (malaise, depression, generalized fatigue and headaches) symptoms, which may persist for months or years (Gillespie *et al.*, 1986; Kodama and Hokama, 1989; Barton *et al.*, 1995; Chan and Kwok, 2001; Arena *et al.*, 2004; Chateau-Degat *et al.*, 2007a,b) make CFP an intensely distressing, and in certain cases, a long term debilitating malady. This may also be alleviated if the treatment is administrated early enough (Lange, 1994; Pearn, 1995; Arena *et al.*, 2004).

As no human biomarker exists to confirm CFP, the diagnosis is entirely based on the clinical scenario and the patient's recent fish-eating history (Blythe *et al.*, 1994; Pearn, 2001; Ting and Brown, 2001) which has often led to treatment delay or omission.

According to certain anecdotal reports, some individuals may occasionally experience recurrence of the main neurological disturbances during periods of overwork, fatigue, stress or with sexual activities (Lange *et al.*, 1992; Bagnis, 1993). Such recurrence have also been reported upon consumption of non-ciguateric fish such as cold-water species and non-fish product such as chicken, pork, canned beef, eggs, nuts, caffeine and alcohol (Gillespie *et al.*, 1986; Gillespie, 1987; Gollop and Pon, 1992; Lange *et al.*, 1992; Bagnis, 1993; Fleming *et al.*, 1997; Lewis, 2000; 2001). The basis of this recurrent attack is unknown but is generally presumed to be an immunologic reaction. The phenomenon of sensitization has also been observed whereby recurrence of symptoms typical of CFP is brought on by the consumption of

Table 6. Symptoms and signs of ciguatera fish poisoning (adapted from Farstad and Chow, 2001).

Gastrointestinal (common/early onset from 2 to 12 hours /lasts 1 to 2 days)	**Cardiovascular (uncommon/early onset/persists up to 1 week)**	**General/Other (Variable occurrence and onset)**
Nausea	Hypotension	Chills
Vomiting	Bradycardia	Perspiration
Diarrhea	Tachycardia	Fever
Abdominal pain	Chest pains	Loss of hair and nails
Hypersalivation	T-wave abnormalities	Conjunctivitis
Painful defecation	Pulmonary edema	Acne
		Skin rash
		Malaise
		Shortness of breath
		Oliguria
		Lacrimation
		Neck stiffness
Neurologic (common/late onset from 12-72 hours*/prolonged symptoms)		
Mental status	***Motor***	***Sensory***
Delirium	Ataxia	Paresthesia (lingual, extremities and circumoral)
Coma	Respiratory arrest	Dysesthesia (arms, legs and perioral region)
Memory/concentration problems	Ophthalmoplegia	Paradoxical dysesthesias
Depression	Seizures	Asthenia
Giddiness	Paresis	Headache
Multitasking difficulties	Diminished reflexes	Myalgia
Hallucinations	Weakness	Dental pain
	Tonic contractions	Photophobia
	Coma	Blindness
		Vertigo
		Arthralgias
		Metallic taste
		Blurred vision
		Pruritus
		Dyspareunia
		Painful ejaculation
		Dysuria
		Mydriasis
		Strabismus
		Desquamation
		Polymyositis

*****Neurological symptoms can occur early in the disease course, but they classically follow gastrointestinal and cardiovascular symptoms.

potentially ciguateric fish that did not produce symptoms in other individuals (Gillespie *et al.*, 1986; Narayan, 1980; Ruff and Lewis, 1994). There is evidence that second and subsequent attacks tend to be more severe than first attacks (Bagnis *et al.*, 1979; Glaziou and Martin, 1993). The basis of the sensitization is believed to be the storage of CTXs in the adipose tissue of victims. Any activity involving increased lipid metabolism may result in CTX re-entering the blood stream (Barton *et al.*, 1995). Similarly, such storage could also lead to an accumulation of the toxins in the host to subclinical levels, each time fish with small amounts of CTX are consumed, thus explaining the severity of subsequent intoxications episodes.

2.5 Pharmacology and Treatment

2.5.1 Mode of action

Pharmacological studies have revealed that CTXs act on voltage-sensitive sodium channels (VSSC) present on most excitable and some non-excitable cells (Rayner, 1972; Lewis *et al.*, 2000; Al-Sabi *et al.*, 2006; Nicholson and Lewis, 2006; Wang, 2008). Like PbTxs, CTXs bind directly to site 5 on the α-subunit of VSSC (Poli *et al.*, 1986; Lombet *et al.*, 1987; Dechraoui *et al.*, 1999), causing them to open at normal cell resting membrane potential. One of the well-established consequences of this activation is the influx of sodium ions (Na^+), which induces membrane depolarization (Bidard *et al.* 1984; Benoit *et al.* 1986) and causes spontaneous firing in a variety of nerve fibers (Bidard *et al.*, 1984; Molgó *et al.*, 1990; Benoit and Legrand, 1992; Benoit *et al.*, 1996; Brock *et al.*, 1995; Hamblin *et al.*, 1995; Hogg *et al.*, 1998). The Na^+ influx results in osmotic deregulation inducing water influx that leads to edema of Schwann cells (Allsop *et al.*, 1986) and axons (Benoit *et al.*, 1996; Mattei *et al.*, 1997; 1999).

Activation of VSSC by P-CTX-1B has also been shown to lead to direct mobilisation of calcium ions (Ca^{2+}) from internal stores (Lewis and Endean, 1986; Molgó *et al.*, 1992; 1993a) and to an indirect activation of the Na^+-Ca^{2+} exchanger allowing Ca^{2+} influx against Na^+ efflux (Molgó *et al.*, 1993b; Gaudry-Talarmain *et al.*, 1996). An

elevation in cytosolic Ca^{2+} may promote neurosecretion believed to underpin certain CFP symptoms (Nicholson and Lewis, 2006; Mattei *et al.*, 2008). Recent studies suggest that CTXs may also modulate voltage-sensitive potassium channels that most likely contribute to membranes depolarization caused by CTX-activated VSSC (Hidalgo *et al.*, 2002; Birinyi-Strachan *et al.*, 2005; Nicholson and Lewis, 2006). Yet another recent study demonstrated the action of CTXs on the L-type calcium channels resulting in the swelling of frog erythrocytes (Sauviat *et al.*, 2006).

Though CTXs seldom accumulate in fish at levels that are lethal to humans, explaining the low mortality, they are extremely potent in that at nanomolar and picomolar concentrations they are able to activate the VSSC in cell membranes (Lewis *et al.*, 2000). Therefore, as sodium channels are widely spread in nerve and muscle tissue, the depolarization of these cells is believed to be the cause of the array of sensorial polyneuropathies and myopathy associated with CFP (Nicholson and Lewis, 2006; Friedmann *et al.*, 2008).

2.5.2 Occidental medicine

The treatment of CFP in the occidental medicine remains mainly symptomatic and supportive. Depending on the clinical symptoms a patient may present; a number of medications are prescribed (Table 7). Intravenous (*i.v.*) D-mannitol infusion is the most studied and the only therapy for CFP evaluated by randomized blinded clinical trials. The therapeutic effect of D-mannitol was fortuitously discovered in Marshall Islands when two men who became unconscious from severe CFP spectacularly responded within minutes after D-mannitol was administrated for presumed cerebral edema. Subsequently, administrated to further 22 ciguatoxic patients, including one with circulatory failure, they found significant relief especially from neurological and muscular dysfunctions (Palafox *et al.*, 1988). Since then, the utilisation of D-mannitol in treatment of CFP has been reported in numerous case reports and trial series from around the world (Williamson, 1989; Pearn *et al.*, 1989; Stewart, 1991; Palafox, 1992; Blythe *et al.*, 1992; 1994; Eastaugh, 1996; Ting and Brown, 2001; Mitchell, 2005; Schwarz *et al.*, 2008; Slobbe *et al.*, 2008).

Currently, accepted as the most effective method of abating the neurological symptoms, D-mannitol, nonetheless, has not been consistently beneficial to all patients. Despite this treatment, the management of the chronic neurological symptoms of CFP continues to be problematic, especially when D-mannitol has not been administrated in the acute phase of the disease (Adams, 1993; de Haro *et al.*, 1997; 2003; Butera *et al.*, 2000). None of the case reports or trial series cited above included a randomized placebo-controlled clinical study, until very recently, whereby the effects of D-mannitol to normal saline were compared in a double-blinded trial (Schnorf *et al.*, 2002). The data obtained indicated that both treatments were associated with clinical improvement and to a similar degree, and that D-mannitol was not superior to saline. Though some clinicians are now beginning to question its efficacy, in the absence of an alternative, the *i.v.* infusion of D-mannitol is still considered the treatment of choice in severe ciguatera intoxications.

Over the years, a myriad of other treatments and medicines, mostly responding to CFP symptoms have been tried (Table 7). The claims of efficiency are again entirely based on small, uncontrolled trial series and case reports. Gastrointestinal symptoms, usually brief and self-limited, require little more than intravenous (*i.v.*) fluid and electrolyte replacement (Gillespie *et al.*, 1986; Cheng and Chung, 2004). In the acute phase of the intoxication activated charcoal, believed to bring some benefit through toxin elimination by absorption, may be administrated. Likewise, gastric lavage (Nicholson and Lewis, 2006), spontaneous vomiting and catharsis, thought to enhance removal of the unabsorbed toxin, are also encouraged (Farstad and Chow, 2001). In the absence of these symptoms, emetics and cathartics are administrated (Gillespie *et al.*, 1986). On the other hand, in certain cases, antiemetic and anti-diarrhea medications may also be prescribed to contain severe gastrointestinal manifestations (de Haro *et al.*, 2003; Cheng and Chung, 2004). For the palliative wellbeing cold showers to relieve pruritus and bed rest during period of convalescence are also indicated. Some clinicians may even advocate a strict diet that avoids all seafood, fish by-products, nuts, nut oil and alcohol for at least 6 months after the intoxication to avoid reappearance of symptoms, and in some cases, patients are asked to abstain from sex (Ruff and Lewis, 1994; Lindsay, 1997; Friedman *et al.*, 2008).

In cases of cardiovascular disorders, atropine is generally used to alleviate hypotension and bradycardia but it has no effect on the neurological or gastrointestinal disturbances. In severe cases, dopamine or adrenaline or calcium gluconate may be required (Baden *et al.*, 1995; Cheng and Chung, 2004; Nicholson and Lewis, 2006). Rarely, critically ill CFP patients may require endotracheal intubation and mechanical ventilation for either airway protection if comatose or in the case of a respiratory failure. Occasionally, in order to manage the dysrhythmias, temporary cardiac pacing may also be inserted (Juranovic and Park, 1991; Ruff and Lewis, 1994; Friedmann *et al.*, 2008). Phenytoin, phenobarbitol or thiopental sodium given *i.v.* has been recommended for the treatment of convulsions (Calvert, 1991).

When the activity of anticholinesterase was held responsible for the toxicity of CTXs (Li, 1965), oxime like pralidoxime was used to reactivate acetylcholine but proved ineffective (Russell, 1975; Morris *et al.*, 1982a). This assertion was later rejected (Rayner *et al.*, 1968; Ogura *et al.*, 1968). On the other hand, some clinicians have used the cholinesterase inhibitors such as neostigmine with a certain success in the severe cases (Banner *et al.*, 1963; Bagnis, 1968).

Other symptomatic treatment includes analgesics for musculoskeletal symptoms. Acetaminophen (paracetemol) has been recommended for relief of headache and indomethacin has been reported to relieve myalgias and arthralgias (Pearce *et al.*, 1983; Calvert, 1991). Their use in chronic CFP is also recommended (Sims, 1987). For generalized pruritus the antihistamines such as diphenhydramine or cyproheptadine are usually prescribed (Gelb and Mildran, 1979; Pearce *et al.*, 1983; Calvert, 1991). But these have been reported to be ineffective in the chronic phase. An *i.v.* use of the corticosteroid, methylprednisolone led to an amelioration of a heightened

Table 7. The occidental medicines prescribed in the treatment for CFP based on anamnesis and the clinical signs that a patient may present.

CFP Symptom Treatment	[a]**Drugs Used**	**Class**	[b]**Prescription/Description**
Neurologic	Vitamins B1	Thiamine	Nutrition supplement - Beriberi characterized by fatigue, depression and loss of appetite that develops to resting tachycardia, decreased deep tendon reflexes, peripheral neuropathy, mental confusion, memory loss, pain in limbs, reduced and involuntary movements.
	Vitamins B6	Pyridoxal	Nutrition supplement - Skin and hair problems, asthma, autism, and cardiac disease related to hyperhomocysteinemia, depression, migraines, kidney stones, muscle pains, epilepsy, multiple sclerosis, neuritis, anemia, and influenza.
	Vitamins B12	Cyanocobalamin	Nutrition supplement - Pernicious anemia characterized by bone marrow promegaloblastosis, gastrointestinal symptoms, neurological symptoms. The neurological complex, defined as myelosis funicularis, consists of impaired perception of deep touch, pressure and vibration, abolishment of sense of touch, very annoying and persistent paresthesia, ataxia of dorsal cord type, decrease or abolishment of deep muscle-tendon reflexes and pathological reflexes (Babinski, Rossolimo and others, also severe). Mental disorders, irritability, focus/concentration problems, depressive state with suicidal tendencies and paraphrenia complex can also occur.
	D-mannitol	Polyol	Diuretic, osmotic – Promotion of dieresis in acute renal failure and urinary excretion of toxic materials, reduction of intracranial pressure and brain mass and of high intraocular pressure.
	Tiapride (Tiapridal®)	benzamide	Antidopamine – relieves intense pain and intero- exteroceptive pains.
	Dexamethasone (Ciprodex®)	glucocorticoid	Antiinflammatory - rheumatoid arthritis, allergic anaphylactic shock, bacterial meningitis, counteract certain side-effects of their antitumor treatment, high altitude cerebral edema as well as pulmonary edema and congenital adrenal hyperplasia.
	Salicyclic acid	beta hydroxy acid	Antiinflammatory - anti-acne, psoriasis, calluses, corns, keratosis pilaris, and warts.
	Paracetamol (Acetaminophen)		Widely-used analgesic and antipyretic medication.
	Amitriptyline	Tricyclic amine	Serotonin and noradrenaline reuptake inhibitor – migraines, vaginal swelling, treatment of depression, nocturnal enuresis, ankylosing spondylitis (a chronic, painful, degenerative inflammatory arthritis primarily affecting spine and sacroiliac joints, causing eventual fusion of the spine) and of certain neuropathic pain, insomnia, anxiety disorders, rebound headache, chronic cough, chronic pain, postherpetic neuralgia (persistent pain following a shingles attack), carpal tunnel syndrome, fibromyalgia, vulvodynia, interstitial cystitis, male chronic pelvic pain syndrome, irritable bowel syndrome, diabetic peripheral neuropathy, neurological pain, and painful paresthesia related to multiple sclerosis and as prophylaxis for frequent migraines.
	Tocainide (Tonocard®)	Lidocaine	Antiarrhythmic – used to correct irregular heartbeats to a normal rhythm by slowing nerve impulses in the heart.
	Gabapentin (Neurontin®)		Antiepileptic – epilepsy, postherpetic neuralgia (neuropathic pain following shingles, other painful neuropathies, and nerve related pain), migraine, headaches, nystagmus and bipolar disorder. Its therapeutic action on neuropathic pain is thought to be brought about by its binding to the voltage-dependent calcium channel in the central nervous system.
	Diphenhydramine (Bendryl®)	Ethanolamine-derivative	Antihistamine - prevents nausea, antitussive, as sleep aid and relieves itching.

Table 7. The occidental medicines prescribed in the treatment for CFP based on anamnesis and the clinical signs that a patient may present.

CFP Symptom Treatment	[a]Drugs Used	Class	[b]Prescription/Description
Digestive	Nifedipine	Dihydropyridine	Calcium channel blocker - its main uses are as an antianginal (especially in Prinzmetal's angina) and antihypertensive, although a large number of other uses have recently been found for this agent, such as Raynaud's phenomenon, premature labour, and painful spasms of the oesophagus in cancer and tetanus patients. It is also commonly used for the small subset of pulmonary hypertension patients whose symptoms respond to calcium channel blockers, Nifedipine rapidly lowers blood pressure.
	Indomethacin		Non-steroidal antiinflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. Since indomethacin inhibits both COX-1 and COX-2, it inhibits the production of prostaglandins in the stomach and intestines which maintain the mucous lining of the gastrointestinal tract.
	Cyproheptadine (Periactin®)		Antihistamine and antiserotonergic – treatment of seasonal and year-round allergies like hay fever, relieves itching and hives, migraine prophylaxis, anorexia nervosa, Equine Cushing's-like syndrome, carcinoid, selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction and hyperhydrosis and used in management of serotonin syndrome. This last condition consists of hyperactive bowel sounds, hypertension, hyperthermia, overactive reflexes, clonus, hypervigilance, agitation, severe hypertension and tachycardia that may lead to shock.
	Neostigmine (Prostigmine®)		Reversible cholinesterase inhibitor - improve muscle tone in people with myasthenia gravis, to reverse the effects of non-depolarizing muscle relaxants after operation, for urinary retention resulting from general anaesthesia, Ogilvie syndrome (a pseudo-obstruction of colon) and to treat curariform drug toxicity.
	Hydroxyzine	piperazine	Antihistamine and anxiolytic – treatment of itches and irritations, of allergic conditions, such as chronic urticaria, atopic or contact dermatoses and histamine-mediated pruritus, is an antiemetic for the reduction of nausea, as a weak analgesic and is also prescribed in general anxiety disorder or in psychoneurosis. A sedative and a mild tranquiliser, it is used in dentistry and in obstetrics.
	Physostigmine	Tertiary amine alkaloid	Reversible cholinesterase inhibitor - treats myasthenia gravis, glaucoma, improves memory in Alzheimer's disease and delayed gastric emptying. Also used to treat the central nervous system effects of atropine, scopolamine and other anticholinergic drug overdoses.
	Fluoxetine (Prozac®)		A SSRI antidepressant - treatment of major depression, obsessive-compulsive disorder, bulimia nervosa, anorexia nervosa, panic disorder and premenstrual dysphoric disorder.
	Lidocaine	Amino-amides	Local anaesthetic and antiarrhythmic – topically used to relieve itching, burning and pain from skin inflammations, also used in postherpetic neuralgia, injected as a dental anesthetic and in minor surgery. Lidocaine alters depolarization in neurons, by blocking the fast voltage gated sodium (Na+) channels in the cell membrane. With sufficient blockade, the membrane of the presynaptic neuron will not depolarize and so fail to transmit an action potential, leading to its anaesthetic effects
	Colchicines	Phenylethyl-amine group of alkaloids	Antimitotic - treatment of rheumatic complaints, muscle spasm, weakness associated with disc disease, gout, also prescribed for its cathartic and emetic effects.
	Pralidoximes	Oximes	Anticholinesterase reactivators – used to combat poisoning by organophosphates or other acetylcholinesterase inhibitors nerve gases.
	Edrophonium		Reversible acetylcholinesterase inhibitor – used to evaluate muscle response and to diagnose and treat myasthenic crisis in order to reduce the muscle weakness. Also employed to reverse the effects of certain muscle relaxants used during surgery. Administrated to patient with atrial tachycardia.

Table 7. The occidental medicines prescribed in the treatment for CFP based on anamnesis and the clinical signs that a patient may present.

CFP Symptom Treatment	**[a]Drugs Used**	**Class**	**[b]Prescription/Description**
Cardio-vascular	Atropine		Anticholinesterase – antidote for nerve agent and organophosphate insecticides intoxication, treatment of bradycardia, asystole, pulseless electrical activity in cardiac arrest and hyperhydrosis, used as a cycloplegic and as a mydriatic, can prevent the death rattle of dying patients. Atropine acts by blocking the effects of excess concentrations of acetylcholine. Generally, atropine lowers the parasympathetic activity of all muscles and glands regulated by the parasympathetic nervous system. It is also used as adjunctive therapy in the management of hypermotility disorders of the lower urinary tract and gastrointestinal system.
	Dopamine	Catecholamines	Neurotransmitter - can be supplied as a medication that acts on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure and in the management of Parkinson's disease dopa-responsive dystonia.
	Calcium gluconate		Mineral supplement - a form of calcium most widely used in the treatment of hypocalcemia. Calcium gluconate is also used as a cardioprotective agent in hyperkalemia. Though it does not have an effect on potassium levels in the blood, it reduces the excitability of cardiomyocytes thus lowering the likelihood of developing cardiac arrhythmias.
	Adrenaline	Catecholamine	Hormone and neurotransmitter - boosts the supply of oxygen and glucose to the brain and muscles. It is a drug of choice to treat cardiac arrest and other cardiac dysrhythmias resulting in diminished or absent cardiac output.

[a] The information on the type of drugs used in the treatment of CFP can be been found in various reviews and articles (Calvert 1991; Glaziou and Legrand 1994; Ruff and Lewis 1994; Farstad and Chow 2001; Ting and Brown 2001 and the articles cited within).

[b]The information on the pharmaceutical drugs and the in dication of use can be found on the online databases Medline Plus; Medscape and Merck Manual.

polymyositis in a case (Stommel *et al.*, 1993). On the other hand, the similarities between the symptoms of avitaminosis B and ciguatera (Boydron-Le Garrec *et al.*, 2005a) have also led to the *i.v.* utilization of vitamin B complex (B1, B6 and B12) in association to *i.v.* calcium gluconate in the treatment of CFP, which reportedly shortened the duration of symptoms (Russell, 1975; Ruff and Lewis, 1994; Glaziou and Legrand, 1994).

Fluoxetine has been used for chronic fatigue and was reported to be effective in two patients suffering from CFP-related chronic fatigue that persisted over nine months (Berlin *et al.*, 1992; Ruff and Lewis, 1994). Occasional diminution of chronic paresthesia and other neurological symptoms has been reported with amitriptyline (Bowman, 1984; Davis and Villar, 1986; Calvert *et al.*, 1987; Lange *et al.*, 1992). However, prescription of these antidepressants with an addiction potential warrants caution (Pagliaro and Pagliaro, 1993; Prahlow and Landrum, 2005; Peles *et al.*, 2008).

Gabapentin, with a known efficacy in neuropathic pain, has recently been reported to improve ongoing polyneuropathic symptoms, chronic dysesthesias and paresthesia, of CFP in two patients (Perez *et al.*, 2001). However, upon discontinuation of this medication, the symptoms reappeared that necessitated a prolonged use. It is not uncommon for the prescription of gabapentin to occur in a mental health context (Berigan, 2000; Carta *et al.*, 2003). Indeed the chronic complaints of CFP (depression, fatigue, algia) can be confounded with psychiatric causes (Arena *et al.*, 2004; Friedman *et al.*, 2007; 2008). Moreover, the sudden discontinuation of gabapentin after long term use may provoke withdrawal symptoms (Tran *et al.*, 2005). Given the persistence of certain symptoms of CFP (Chateau-Degat *et al.*, 2007a; 2007b), prescriptions of this substance thus necessitate caution on the part of clinicians.

Tocainide, an analogue of lidocaine safely alleviated ciguatoxic symptoms in three adult males (Lange *et al.*, 1988), while nifedipine has been noted for the resolution of headaches in a patient (Calvert *et al.*, 1987). These drugs, the lidocaines analogs (tocainide and mexiletine) as well as amitriptyline and fluoxetine, and nifedipine and gabapentin appear to alter the Na^+ and Ca^{2+} channels, respectively, and hence are of theoretical appeal in CFP (Nicholson *et al.*, 2002; Nicholson and Lewis, 2006).

Nevertheless, like pyridoxine, diazepam, pralidoxime and protamide, the clinical use of all of these agents in CFP are very limited and have responded with variable success (Farstad and Chow, 2001, Raikhlin-Eisenkraft and Bentur, 2002; Cheng and Chung, 2004). The efficacy of these agents like D-mannitol in humans as consequence still needs to be proven. As none of these palliative treatments are wholly remedial, Pacific Islanders resort regularly to traditional form of care (Banner *et al.*, 1963; Bourdy *et al.*, 1992; Laurent *et al.*, 1993).

2.5.3 Traditional medicine

Over the centuries the primeval people of the Pacific, where CFP has the highest occurrence, have elaborated, through trial and error, a variety of traditional herbal medicines and remedies. Today the insular population continues to employ this ancient pharmacopoeia in the treatment of CFP. In view of the growing socio-economical gravity of CFP in insular nations (Bagnis, 1992; Dalzell, 1992; Laurent *et al.*, 2005) and the desistance of use of medical care due to frequent deceptions, poor financial resources and the geographical isolation of several Pacific islands, the use of alternative therapy is extremely popular (Barrau, 1950; Haddock, 1973; Rageau, 1973; Dufva *et al.*, 1976; Lobel, 1979; Bourret, 1981; Vienne, 1981; Laurent *et al.*, 1993; Cabalion, 1984a; 1984b; 1984c; 1984d; 1984e; Bourdeau, 1985; Weiner, 1985; Pétard, 1986; Bourdy *et al.*, 1992; Laurent *et al.*, 1993). Similarly, the population of other regions touched by CFP, the Caribbean Sea and the Indian Ocean, also avails to such therapies (Kaplan, 1999).

In the early 1990's, a 10-year long ethnopharmacological survey carried out on the various islands of New Caledonia and Vanuatu resulted in an inventory of at least 90 different plant species used in the preparation of folk remedy against CFP (Bourdy *et al.*, 1992; Laurent *et al.*, 1993). This study provided excellent accounts on the parts of the plants used and the mode of preparation and administration of these phytotherapies. However, despite the effort on the part of the authors, the information on the dosage and the duration of each treatment could not be clearly reported due to the large variations in the data collected from one traditional healer to another.

Nonetheless, this survey has provided precision on the nature of use of these phytotherapies, that is if the mode of practice is curative or preventive or both. As means of prevention when a fish is suspected, certain plants based on believe to be capable of neutralizing the causative toxins are introduced in the culinary preparation or are consumed together with the fishmeal. However, the majority of these plants are used as therapeutics. Indeed, reputed for their general purgative, antidiarrhoeal, antirheumatic, antipruritic and analgesic effects, their utilization in the treatment of CFP is most probably symptomatic rather than by a specific detoxification process (Bourdy *et al.*, 1992; Laurent *et al.*, 1993). This may explain the important number of plants used in relation to the several symptoms that are provoked by this intoxication.

Among the plants administrated as symptomatic, *Heliotropium foertherianum* (formerly *Argusia argentea*), *Cocos nucifera*, *Erythrina variegata* var. *fastigiata*, *Punica granatum*, *Syzygium malaccense*, *Artocarpus altilis*, *Carica papaya*, *Pandanus tectorius*, *Terminalia catappa*, *Vitex rotundifolia* and *Scaevola sericea* are much more often used than others throughout Polynesia and/or Melanesia (Bourdy *et al.*, 1992; Laurent *et al.*, 1993). Believed to possess depurative activities, the use of the plant *H. foertherianum* in CFP, particularly popular in the Western Pacific Basin has also been reported in island nations of French Polynesia, Tonga, Micronesia and Japan (Banner *et al.*, 1963; Hashimoto *et al.*, 1969; Bagnis, 1973; Halstead 1978; Bourdy *et al.* 1992, Laurent *et al.* 1993; Noro *et al.*, 2003). In order to evaluate the anti-ciguateric potential of these plants, several scientific experiments were pursued in various biological models. These are discussed in detail below.

Following the ethnobotanical survey, the very first evaluation of the phytotherapies was undertaken in a mouse bioassay (Amade and Laurent, 1992). Based on the

popularity of use, facility of identification and collection and a probable action on the nervous system, *H. foertherianum* and twenty of other plants (*C. nucifera*, *T. catappa*, *C. papaya*, *S. malaccense*, *A. altilis*, *Vitex rotundifolia* var. *subtrisecta*, *P. granatum*, *E. variegata* var. *fastigiata*, *Schinus terebenthifolius*, *P. tectorius*, *Morinda citrifolia*, *Acacia spirorbis*, *S. sericea*, *Ipomoea pes-caprae* and the less popular *Davallia solida*, *Plectranthus parviflorus*, *Polyscias scutellaria*, *Xylocarpus granatum*, *Ximenia americana* and *Euphorbia hirta)* were selected. The extracts from these plants were prepared according to the traditional method and their effects were evaluated in mice intoxicated *via* intraperitonal (*i.p.*) injection with a sublethal dose of a liver extract obtained from *G. javanicus*. The toxic extract provokes a significant corporal weight loss in mice over 24 to 48 h, after which the growth curve normalizes, indicating a recovery. A significant reduction in the weight loss and amelioration in the recovery time was observed in mice co-treated with the leave extracts of *H. foertherianum* and *S. terebenthifolius*, in contrast to *i.v.* D-mannitol, tocainide and the other plant extracts tested (Amade and Laurent, 1992; Laurent and Amade, 1992). Based on these results, the therapeutic potential of these two remedies in the cure of CFP were suggested.

However, this study only allows a semi-quantitative evaluation of the activity of the extracts, in that it provides no information as to how this beneficial effect is produced. In addition, though, mouse bioassay has been standardized and is widely used as a CTX detection method (Vernoux, 1994; Boydron-Le Garrec *et al.*, 2005b), here as a biological test it poses certain limits. The authors stated that they were confronted with two major inconveniences with this study. First, the results were not reproducible, varying from an individual to other, which necessitated the use of an important number of animals and second, unlike human subjects, the mice did not present signs of intoxication after 24-48 h (Laurent and Amade, 1992). Indeed, based on pharmacokinetic observations with PbTxs, rodents are believed to rapidly eliminate CTXs from their organism (Poli *et al.*, 1990; Radwan *et al.*, 2005). The relatively shorten convalescence and the refractoriness of mice to the effects of CTXs indicate that the end point of this bioassay may not represent a classical response in humans (Higerd, 1983). This is further substantiated by the fact that axonal edema reported on nerve biopsy in human with ciguatera intoxication is absent in the mice models (Lewis and Endean, 1983; Lewis *et al.*, 1993). However, axonal edema due to CTXs has been observed in *in vitro* myelinated nerves of frog (Benoit *et al.*, 1996, Mattei *et al.*, 1997; 1999).

Consistent with the neurological alterations reported in patients suffering from CFP, the exposure of frog axon to CTXs results in high frequency action potential discharges and perturbations in osmotic balance causing water influx leading to a marked increase in cellular volume (Benoit *et al.*, 1996). The fact that this edema was prevented by tetrodotoxin (TTX), a potent VSSC inhibitor, underlines the role of the continuous Na^+ influx in the swellings observed in the nodes of Ranvier and motor nerve terminals. Inspired from experiments effectuated with D-mannitol, the positive effects of the leaves and root extract of *H. foertherianum* and *D. solida*, respectively, against the P-CTX-1B-induced electrophysiological and morphological alterations in frog myelinated axons were confirmed. Like D-mannitol, the spontaneous and repetitive action potential firing in the nodal membrane and the edema of node of Ranvier resolved upon co-treatment with these two plants. Remarkably, when the axons were washed, the inhibitory action of *D. solida* on the spontaneous repetitive action potentials as opposed to that of *H. foertherianum* proved to be irreversible (Benoit *et al.*, 2000).

As these neurocellular tests require highly specialized material and hours of preparation, which is not compatible with bio-guided chemical fractionation evaluations, a simpler test was developed based on the morphological alteration of frog erythrocytes induced by the osmotic effect of P-CTX-1B. In this bioassay, the leave extract of *H. foertherianum* was able to suppress the swelling induced by the toxin, as observed by the reduction in apparent surface area of the treated erythrocytes.

As opposed to the CTXs-induced edema in frog axons, TTX was not able to reverse the CTXs-induced swelling in frog erythrocytes. In addition, an augmentation in the volume was observed when Ca^{2+} was added to the physiological medium, indicating an entry of Ca^{2+} rather than Na^+ (Boydron *et al.*, 2001). Further molecular investigation on this model demonstrated that the entry of Ca^{2+} resulted from the activation of the L-type calcium channel and that the cascade of events leading to the swelling of erythrocytes may involve the activation of the enzyme nitric oxide synthase (Sauviat *et al.*, 2006).

Eventually this test was further adapted. The frog erythrocytes were replaced with human red blood cells and the hemolytic activity of P-CTX-1 was studied. In this bioassay similar results were obtained with *H. foertherianum* and TTX (Boydron *et al.*, 2002). However, as the event of hemolysis of the red blood cell does not seem to depend on the activation of VSSC and as the bioassay itself lacked in sensitivity, another biological test was elaborated using established nerve cells derived from a mouse brain cancer. This murine neuroblastoma (Neuro 2a) cell line is known to express the VSSC proteins, which when challenged with veratridine and ouabain induces cytotoxicity that is further potentiated by PbTx-3 or P-CTX-1 (Manger *et al.*, 1993; 1994; 1995). Veratridine (site 2 VSSC activator) causes sodium channels in the cell membrane to open allowing a potentially lethal influx of sodium ions into the cells. Ouabain (Na^+/K^+- pump inhibitor) inhibits the action of a transporter that pumps sodium ion back out of the cell and so maximizes the effect of veratridine. The PbTx-3 and P-CTX-1, being sodium channel activators, enhances the effects of veratridine on sodium ion influx, causing cellular swelling and subsequent death (Nicholson *et al.*, 2002). In this way, it was possible to study the counteractive effects of 31 and 7 plant extracts against the cytotoxicities induced by ouabain, veratridine and PbTx-3 or P-CTX-1, respectively.

Among the 24 plant extracts that exhibited by themselves no toxicity in Neuro 2a cells, 22 prevented the cytotoxicity due to one or more Na^+ channel modulators applied. Based on numerous controls, the anticytotoxicity activities of certain extracts (*S. malaccense*, *A. altilis*, *Stachytarpheta australis*, *Capsicum frutescens*, *X. americana*, *M. citrifolia*, *Dendrolobium umbellatum*, *P.*

tectorius, *V. rotundifolia* var. *subtrisecta* and *I. pes-caprae*) against the toxicity of PbTx-3 were differentiated from those of the potentiating agents used. Subsequently, the plants *E. hirta*, *S. sericea*, *S. malaccense*, *S. cytherea*, *A. altilis* and *S. australis* were also shown to strongly counteract the cytotoxicity induced by P-CTX-1 and the two ionic modulators, ouabain and veratridine (Boydron-Le Garrec *et al.*, 2005c).

3. Discussion and Conclusion

Marine algal toxins impact human health essentially through seafood consumption and in the case of NSP also *via* the respiratory routes. With the increasing use of marine organisms for human consumption, human at the top of the food chain is more likely to encounter these toxins. Among the six well-characterized seafood poisoning syndromes discussed in this review, CFP is by far the most common form of intoxication. Had it not been for this man's appetite for fish, the story of CFP might have remained a secret of coral reef ecology. As intuitively foreseen by Jacques Grevin (Grevin, 1568), a French physician and poet, the research on ciguatera has been painstakingly slow. Though, a considerable progress has been made in the last few decades requiring concerted efforts from scientists from multidisciplinary fields, this has yet to be translated into the development of an effective therapy. This also holds true for the other seafood-associated syndromes described in this review.

With the highest incidence in the Pacific region, CFP is an exceedingly unpleasant illness that represents a serious socio-economic problem in these island nations that depend heavily on fish products for their livelihood and where the toxins involved are the most potent. Though various medicines have been and are still used for the treatment of CFP, the efficacy of these agents remains uncertain. Thus at present, prevention through the avoidance of eating fish or fish part that have a greater likelihood of ciguatoxicity appears to be the only solution. Yet in the absence of a reliable, cost-effective method of detection of CTXs in fishes, prevention has also proved to be difficult. In certain islands, the high incidence of CFP has driven the population to abstain completely from consuming fresh fishes from their lagoons (Fleming and Eason, 1998). This has also led to loss in economy due to imposed exportation embargos (Laurent *et al.*, 2005). Hence, it is evident that there was an urgent need to establish a therapeutic regime.

Given the popular use of traditional medicine in the Pacific, various studies reviewed herewith on certain of the plants used in the treatment of CFP gave evidence of their efficiencies against the noxious effects of CTXs in *in vitro* and *in vivo* models. However, target-based and quantitative pharmacological evaluation of potentially bioactive molecules in the plants having the specific effect against the action of CTXs in the human biological system has been hampered by the scarcity of CTXs and inappropriate and impractical bioassays. It is in this regard, that the bioassay with Neuro 2a cells was adapted in 2004 to evaluate the therapeutic potential of plants. Originally develop ten years earlier to detect CTXs, PbTXs and saxitoxins in fish and microalgal samples, this biological method at that time presented an ideal approach to perform high volume screening for the identification of potentially active plants and eventually compounds possessing therapeutic activities against CFP. Though rapid and replicable, this semi-automated biological assay for the purpose of therapeutic evaluation lacks in specificity and clinical consistency.

Indeed, without ouabain and veratridine co-treatment, the Neuro-2a cells were resistant to the effects of CTXs and PbTxs, exhibiting extremely low to insignificant cytotoxicities. The co-addition of these potentiating agents in detection bioassays though may serve as an indicator for the presence of VSSC activator toxins in biological samples, in experiments evaluating therapeutic activity of plants; however, addition of these pharmacologically active agents is not a true reflection of the conditions of clinical CFP intoxications in humans. This raises questions on suitability and specificity of this biological assay for the tests with plants. Despite the discriminatory controls, the phenomenon of synergistic effects is complicated. Thus the extrapolation of the results obtained from this model to clinical situations may not be reliable.

Hence though this bioassay has provided valuable information of therapeutic potential of the plants, other biological approaches adapting more closely the pharmacological action of CTXs are necessary to provide further scientific-based evidence of the efficiency of plants with assurance of specific clinical efficiency in the treatment of CFP. Furthermore, given the extreme rarity of CTXs it is also important that these bioassays are miniaturized and/or permit the replacement of CTXs with other easily available functional agents like PbTxs. These bioassays should also be practicable, rapid and reproducible, allowing medium to large-scale screening and bio-fractionation studies with relative ease and which will subsequently allow the isolation of a number of new bioactive molecules from the plants.

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