 doi:10.20944/preprints202007.0446.v1

Review

Epidemiology and toxicology of Ciguatera poisoning in the Colombian Caribbean

Roberto Navarro Quiroz [1], Juan Carlos Herrera-Usuga[2], Laura Maria Osorio-Ospina[2,3], Katia Margarita Garcia-Pertuz and Elkin Navarro Quiroz [3],*.

1 CMCC-Centro de Matemática, Computação e Cognição, Laboratório do Biología Computacional e Bioinformática–LBCB, Universidade Federal do ABC, Sao Paulo, 01023, Brazil;

2 School of Medicine; Universidad de Cartagena, Cartagena, 130001, Colombia;

3 School of Medicine; Universidad Remington, Medellin, 050001, Colombia

4 School of Medicine; Universidad del Norte, Barranquilla, 080001, Colombia.

5 Faculty of Basic and Biomedical Sciences, Universidad Simon Bolivar, Barranquilla, 080001, Colombia;

6 Nephrology, Clinica de la Costa, Barranquilla, 080001, Colombia;

7 School of Medicine, Universidad San Martin, Puerto Colombia, 081007, Colombia Department of

* Correspondence: enavarro26@unisimonbolivar.edu.co; Tel.: +57-3015987517

;

* **Correspondence: enavarro26@unisimonbolivar.edu.co; Tel.: +57-3015987517**Received: date; Accepted: date; Published: date

Abstract: The ciguatera is a food poisoning caused by the consumption of primarily coral fish; these species exist in large numbers in the seas that bathe the Colombian territory. The underreported diagnosis of this clinical entity has been widely highlighted due to multiple factors, as are among others, ignorance by the primary care practitioner consulted for this condition, clinical similarity with secondary gastroenteric symptoms, to common food poisonings of bacterial, parasitic or viral etiology. Eventually people affected by ciguatotoxin are related to trips to coastal areas hours before the onset of symptoms. Thanks to multiple studies over the years it has been possible to identify the relation of the dinoflagellates in the assembly of said toxin and its introduction into the food chain, starting by fish primarily inhabiting reef ecosystems and culminating in the intake of these by humans. Identifying the epidemiological link, its cardinal symptoms and affected systems such as gastrointestinal, peripheral nervous system and fortunately with a low frequency, the cardiovascular system, leads to a purely clinical diagnostic impression without further complementary studies, performing an adequate treatment primarily symptomatic without underestimating or overlooking any associated complications.

Keywords: Ciguatotoxin, dinoflagellates, intoxication, mannitol

1. Introduction

 doi:10.20944/preprints202007.0446.v1

Ciguatera is intoxication for ate contaminated fish with dinoflagellate's ladder frame polyether toxins, Ciguatera fish poisoning (CFP) are polyether ladder-formed toxins produced by several species of diatom and dinoflagellate [1], the main genus associated with ciguatoxins produced is *Gambierdiscus*, addition to *Gambierdiscus* in colombia have been reported other genus such as: *Actinocyclus, Nitzschia, Rhabdonema,* and *Thalassionema* [2]. CFP were first isolated in 1967 from *Gymnothorax javanicus*[3], in 1989 the Ciguatera was postulated that its accumulated in fish throughout the food webs, as well as, it was elucidated the structure of CFP[4]. The structures more described is Caribbean ciguatoxin (C-CTX-1) and its molecular formula is $C_{62}H_{92}O_{19}$ [5].

On the other hand, the epidemiological(affects up to 50,000 people each year throughout the world) effects of ciguatera have a great impact on the tourist and gastronomic sector in the Colombian Atlantic and Pacific coast so that they have been described in the Colombian Caribbean that main cause of the ciguatera event consumption of barracuda meat (Sphyraena barracuda) and moray eel (Gymnothorax moringa) [6].

Regarding the first historical record of the reported case of ichthyosarcotoxicosis in Colombia, caused by ingesting the meat of a slender amberjack (*Seriola zonata*) does not leave on the presence of dinoflagellates with toxic properties in waters adjacent to the departments of Bolívar and Sucre in the Caribbean Colombian. The slender amberjack (male, 4-5 kg, 400-500 mm in length) was captured using trolley during a sport fishing contest organized by the Cartagena Fishing Club off the coast of the departments mentioned in Bajo Fríjol, approximately 12 miles from Tortua Island on July 5 th, 1994[7].

There is little information on ciguatera poisoning in Colombia and the registration of the dynastic is difficult, given that Colombia is not required to register for the National Public Health Surveillance System -SIVIGILA and for ease as signs and symptom, For this reason, this review aims to make a survey of the ciguatera register in the Colombian Caribbean and the development of cases recorded when it was possible to find this description.

Epidemiology in Colombia

Ciguatera fish poisoning is prevalent worldwide, estimated more than 50,000 cases in the world. In the Colombian territory it is not part of the mandatory notifiable diseases, it is important to know the origin of Ciguatera fish poisoning which is synthesized by a group of microalgae called dinoflagellates of which around 50 species are producers of Ciguatera fish poisoning, their distribution in cosmopolitan, in their habitat they cover surfaces of reefs and macroalgae[2].

A study carried out by the National University of Colombia department of biology evaluated the presence of potentially toxic Dinoflagellates associated with floating organic material in San Andrés Islas(drif), The results indicate that drift is an important substrate for dinoflagellates (*Prorocentrum emarginatum* and *Sinophysis microcephala)* and given its floating nature, it represents perhaps the most important vector for the dispersion of these toxic agents on the island[8].

Regarding the records of ciguatera poisoning on the island of San Andrés , two outbreaks were recorded in 1997, which affected 16 tourists and 9 residents, In the island of San Andrés the presence of epiphytic toxic dinoflagellates in the seagrass meadows of the northern and eastern sectors of the island in coastal waters, the most abundant species was *Ostreopsis ovata*, had a density of 23 cells/grams dry weight [9].

On the other hand, an ichthyotoxin poisoning event is described in the fishing community of the city of Tasajera, department of Magdalena. Ciguatera poisoning was diagnosed in 7 individuals whose ages ranged from 17 to 53 years (63.4% of the age range of fishermen in the sector), with symptoms of vomiting (100%), muscle pain in the lower extremities (71 , 4%), abdominal spasms (85.7%), diarrhea (100%), numbness and tingling in the face, hands, feet (85.7%), dizziness (100%) and rash (14.2%), symptoms in most cases disappeared within 8 to 12 days. The main cause of the ciguatera event was the consumption of barracuda (Sphyraena barracuda) and brown meat (Gymnothorax moringa)[10].

In April 2007, in San Andrés, two ciguatera outbreaks occurred with 9 and 16 people involved (residents and tourists respectively) after ingesting barracuda. The intoxicated presented

 doi:10.20944/preprints202007.0446.v1

paraesthesia in upper and lower limbs, tetany in hands and feet, pruritus, malaise, vomiting, respiratory distress and / or diarrhea[11].

Between 2010 and 2014, 101 cases of ciguatera in the department of San Andrés and Providencia were notified to the Public Health Surveillance System of the National Health Institute, with no associated mortalities. 14 isolated cases and 87 cases associated with 21 outbreaks were reported; On average, each outbreak affected 4.1 people and 20.2 cases were reported annually[11].

In 2017 Steven R. and collaborators reported Ciguatera fish poisoning (CFP) incidence rates (per 100,000) and mean projected growth rate (div. mo−1) for the Gambierdiscus species composite incidence rates, however, average zero to 0.02 per 100,000 in Colombia[12].

In the Colombian Caribbean, more than 200 cases of ciguatera have been reported since 1968, without deaths[13].

Table 1..Number of outbreaks and cases of ciguatera reported between 1968 and 2015

year	Number of shoots	Number of cases associated with outbreaks	Number of isolated cases	total
1968	1	28	0	28
1984	1	15	0	15
1994	1	7	0	7
1997	2	25	0	25
2005	1	7	0	7
2007	2	25	0	25
2010	5	28	0	28
2011	1	9	0	9
2012	3	12	2	14
2013	9	30	3	33
2014	3	8	9	17
2015	1	30	0	30
total	30	224	14	238

Distribution of dinoflagellates associated with ciguatoxin in the Colombian coasts

Regarding the richness and abundance of dinoflagellates associated with the production of CFP in Colombia, some studies have been described in which they are described:

In 2015, was determined the composition and abundance of dinoflagellates associated with seagrasses they collected 18 samples on Isla de Barú, found ten diatom genus and three dinoflagellate genus, Prorocentrum, Ostreopsis, and Gambierdiscus, that include toxigenic species related to ciguatera and diarrheic shellfish poisoning. Prorocentrum lima was the most abundant dinoflagellate, with average cell densities of 52±48 cells/g substrate wet weight. The temperature hypothesis gains strength as one of the main modulators of dinoflagellate abundance observed in the Caribbean, especially regarding Prorocentrum species and some diatoms such as Mastogloia corsicana and Actinocyclus normanii [2].

Three species of seagrasses, Thalassia testudinum, Syringodium filiforme and Halodule wrightii, were found on Isla de Barú, and T. testudinum was the most abundant and dominant. Although the cell densities of epiphytic dinoflagellates found on Isla de Barú in April and September of 2015 did not show statistically significant differences between sites or months of sampling ($p>0.05$)[2].

 doi:10.20944/preprints202007.0446.v1

In 2010, Rodriguez, J *et al* studied in the island of San Andres, dinoflagellates associated with *Thalassia testudinum,* they found seven species of dinoflagellates (*Ostreopsis ovata, Prorocentrum emarginatum, Prorocentrum lima, Prorocentrum hoffmannianum, Prorocentrum maculosum, Prorocentrum rathymun* and *Sinophysis microcephala*) with a cell densities mean 166 cells / grams dry weight, divided between eight sites(Rocky Cay, Mar Azul, Bahía Honda, Harbor, cotton cay, Isleño, Toninos and Acurio) [9].

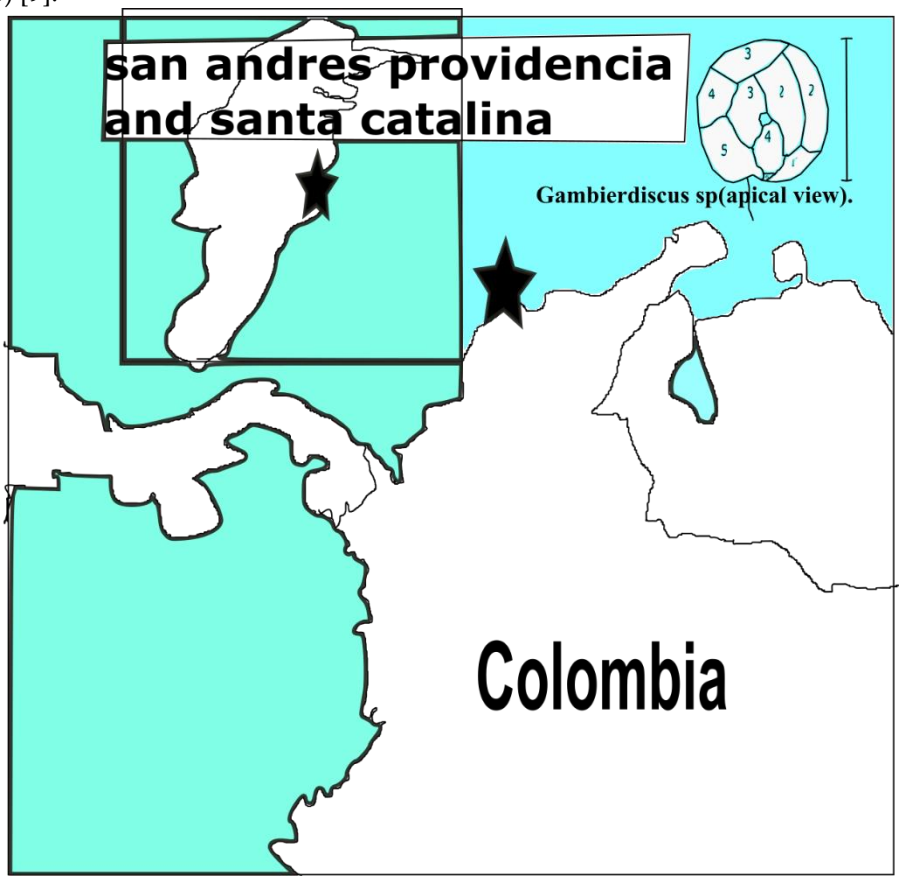

Figure 1.Colombian Atlantic coast and at the top a dinoflagellate representative of the Gambierdiscus sp(each of the 6 plates that are distinguished in the apical view, the bar represents 200 micrometers)(the stars represent places where CFP cases are reported).

Pathophysiology

The *Gambierdiscus toxicus* is the dinoflagellate most associated with the production of ciguatotoxin that is the cause of systemic symptomatology [14]. This toxin is of lipid nature, formed rings joined by ether bonds that gives them firmness in its structure. Identified three types of ciguatotoxins P-CTX1, P-CTX2, P-CTX3 which accumulate more frequently in muscle, liver, kidneys, and spleen of bioaccumulated fish. It presents intrinsic resistance to cold, heat, exposure to acidic and basic media, therefore cooking contaminated fish is not a guarantee for the prevention of toxic infection [15].

The intoxication is result of eat herbivorous fish that its main form food are dinoflagellates and their toxins are consumed and bioaccumulate by these seconds [16].

Several factors influence the risk of acquiring of being intoxicated, being more viable when consuming large or long-lived fish because they are the largest accumulation of toxins [17], it should be noted that bioaccumulated fish have a normal appearance, texture, smell and tasting [18].

As for toxicokinetics of CFP, many details remain to be clarified, however it is known that its intestinal absorption is rapid, it is quickly located in white tissues such as skeletal muscle, heart and nervous system, it is transported together with plasma proteins, mainly seroalbumin, it can be Finding toxin levels in body fluids such as breast milk and seminal fluid, in addition to its

 doi:10.20944/preprints202007.0446.v1

characteristic of liposolubility, crosses the placental barrier and can cause fetal conditions with aborted during the acute phase of the poisoning , After a liver biotransformation finally, the toxin is excreted by bile and feces [19].

Toxicodynamics consists of an induction to the opening of Voltage-gated sodium channels dependent on CFP at the level of skeletal muscle, heart cells and mainly peripheral nerves, once the open sodium channels an intracellular flow of sodium is generated, with this allow water to enter the cell and produce edema generated at the level of the white tissues by the toxin mentioned previously. In search of intracellular homeostasis, compensatory mechanisms begin the expulsion of excess sodium internalized in the cell, exchanging it for extracellular calcium to such an extent that intracellular calcium levels can become so high that they generate increased tissue contraction force muscle[20].

Clinical manifestations

The general signs and symptoms of CFP are as follows: headache, diarrhea, vomiting, osteotendinous hyporeflexia, hives, conjunctivitis, pain, and decreased visual acuity. These clinical presentations may vary in the acute, chronic, and relapsing phases of the illness[21].

According to the article of Palafox, N. A., & Buenconsejo-Lum, L. E. in 2001[21], the clinical manifestations are divided space time in: Acute (within the first two weeks of exposure of ciguatoxin), Chronic(that persists beyond two weeks of the initial intoxication) and relapsing phases of the illness(occur years after the initial intoxication)[21].

Looking at the first symptoms detected from the CFP frequently appear 4–6 hours after toxin consumption, but can occur within minutes with large toxin ingestions or can manifest in 24 hours with smaller doses of toxin[22].

The disease given by ciguatotoxin presents a great variety of symptoms whose behavior may even depend on the region where it is ingested, it is said that the Caribbean areas have primarily gastrointestinal symptoms on the neurological ones, the opposite happens in the Pacific[23]. Symptoms usually begin minutes after ingestion, however, cases of late onset with more than 36 hours have been described; For unknown reasons it has been observed that people who ingest fish contaminated with ciguatotoxin do not present any condition[24]. More than 175 symptoms related to toxic infection have been described, the following will emphasize the most common[25]:

Gastrointestinal tract: It is perhaps the most affected and earlier onset, it is characterized by diarrhea, nausea, vomiting, metallic taste, abdominal pain, and pain with defecation. Easily appearing a gastroenteritis of infectious origin, they are very nonspecific symptoms that usually do not orient the ciguatera disease with certainty, they can take a long time to disappear, usually between 1 and 2 days post-intake[26].

Neurological manifestations: They are the ones that most suspect the diagnosis, based on the pathophysiology of the toxin when producing sodium channels opening, with large intracellular water flow causing edema at the level of schwan cells and axons generating decrease in the speed of nerve conduction and increase of the refractory phase of the potential of the action, therefore the patients present paresthesias in limbs that could start from 30 minutes or days after the consumption of the contaminated fish, being able to persist for months or years, in addition cases of odontalgias have been reported , ataxia, vertigo, allodynia and headache after consumption of ciguatotoxin[27]–[29].

Cardiovascular Manifestation : they are the least frequent but the most feared, usually start 2 and 3 days after consumption[30]. The toxin has a direct effect on the papillary muscles and on the atrium therefore predisposes the patient to presenting cardiac arrhythmias, extrasystoles and heart failure that can be potentially lethal. Orthostatic hypotension due to stimulation of the parasympathetic system and respiratory arrest due to phrenic nerve block has also been described[31].

Other manifestations: the most frequent skin conditions of toxic infection are rash associated with pruritus and are related to acne exacerbations[12].

 doi:10.20944/preprints202007.0446.v1

The main route of acquisition of the toxin is orally, there are other ways of transmission such as maternal-fetal with which cases of abortions and preterm birth have been reported, in addition to the sexual route by the presence of the toxin in the liquid seminal causing pain during ejaculation, vaginal burning, pelvic pain, symptoms that may persist for 2 to 3 weeks[32].

Diagnosis

The diagnosis is clearly clinical, the recent history of fish consumption, more if they are species of reef with subsequent onset of a gastroenteric condition associated with neuropathic symptoms mainly at the level of peripheral nervous system; It should always be remembered that the consumption of fish in non-coastal areas does not exclude the diagnosis[33].

The results of general paraclinics such as hemogram, arterial gases, renal and hepatic function generally yield results in the normal range. Nonspecific alterations in heart rhythm documented in electrocardiogram traces should generate suspicion about the cardiac compromise generated by ciguatotoxin[34].

So far there is no specific paraclinical method for accurate diagnosis of ciguatera in humans A practical product is commercialized to detect toxins in the meat of the fish to be consumed, called ciguaCheck[34], [35].

It is worth mentioning the most traditional biological method, with considerable reliability without being highly specific, that due to its high cost it is not considered a routine diagnostic method that is available for use in most care centers, nor is it cost effective. This is the mouse bioassay where the rodent is fed with contaminated fish meat where one of its main disadvantages is the long observation time of the mice that consumed the contaminated fish meat[36], [37].

Differential diagnoses

Like ciguatera, there is a wide range of toxic infections related to consumption of seafood that are the same or mostly unknown and whose clinical manifestations can be very similar[38].

Tetradotoxism caused by tetradotoxin that is acquired by consuming puffer fish is the most fatal marine toxin causing systemic block of sodium channels generating symptoms on approximately 20 minutes up to 3 hours after ingestions with rapid evolution taking nausea, vomiting, headache , paraesthesia, dysarthria, ataxia, quadriplegia, respiratory failure, coma and death. There is no evidence of an antidote, treatment consists of limiting or minimizing absorption and treating complications that threaten the patient's life[39].

The scombroidosis caused by the consumption of fish that have not had a good refrigeration, begins a process of decomposition with growth of bacterial colonies activating the enzyme histidine decarboxylase using as a substrate histidine, abundant amino acid in the muscle tissue of reef fish[40], with the end product of the enzymatic activity, a large amount of histamine is generated, which is absorbed and distributed at the systemic level of the person affected, generating symptoms such as flush, rash, pruritus, nausea, vomiting, diarrhea, headache, injection between minutes. conjunctival, cough, bronchospasm, tachycardia and anaphylactic shock[41].

Treatment

Treatment consists of adrenaline in cases of anaphylactic shock, corticosteroids and antihistamines[42].

Additionally in initial treatment with mannitol may be considered, although the mechanism is not clear, it can be used in patients with significant morbidity due to poisoning by ciguatera fish[43].

Food poisoning of bacterial, viral or parasitic etiology, can be triggered by consumption of contaminated fish during the process of handling these foods, often associated with dysentery and fever, are not related to neurological symptoms except for botulism caused by intake of clostridium botulinum toxins[1].

The clinical management of ciguatera poisoning is symptomatic and supportive, it should be noted that the topic should be known and that it exists so as not to underreport such poisoning, in

 doi:10.20944/preprints202007.0446.v1

the following section a division between acute management and chronic management will be performed[1].

Acute Management

Patient with symptoms with skin rash associated with pruritus plus acute gastroenteritis, his medical management is with isotonic intravenous fluids such as 0.9% saline solution or ringer's lactate according to the state of dehydration in which the patient is associated to it is added a antiemetic plus antihistamines for local symptoms[44].

There are case reports in which patients have severe poisoning defined as alterations in the state of consciousness, presence of cardiac arrhythmias and / or hypotension, in these cases it must be started by ensuring the airway if necessary and starting early mannitol at a dose of 1gr / kg of weight to pass in 30 minutes to 1 hour and the dose can be repeated, as such its mechanism of action is not known exactly but it has been speculated that due to its osmotic diuretic effect it sweeps with ciguatotoxin and decreases the Axonal edema for causing competitive inhibition with sodium channels, for the beginning of said diuretic should not wait more than 72 hours[44].

In cases of hypotension, supportive medical management with dopamine and antishock therapy with volume expanders can be initiated, in case of bradycardia atropine at a dose of 0.5-2mg intravenously is useful[45].

Chronic management

As for chronic management, it should be noted that all treatments are aimed at neuropathic therapies, since the predominant symptoms are from the peripheral nervous system, for example, paraesthesia, dysesthesia, vertigo, multiple drugs have been studied for these symptoms, currently they are used with little clinical evidence, pregabalin, gabapentin, calcium channel inhibitors such as nifedipine, amitriptyline as a sodium channel membrane stabilizer. It must be said that the management of chronic symptoms could be long term and in some circumstances, it becomes a challenge for the clinician[46].

3. Conclusions

Ciguatera poisoning is a disease with great impact on public health especially in Colombian coast, the most frequently given advice is not to consume fish weighing more than 2 kg, avoid eating fish such as barracuda and not eating fish parts such as viscera, brain and gonads which is where ciguatotoxin is mostly accumulated. An invitation is made for the territorial entities to carry out control measures in the consumption of certain fish, in addition it is a medical and environmental alert, the symptoms must be known and an adequate diagnosis of this poisoning that really does not escape from our daily life.

4. Patents

Author Contributions: Conceptualization, E.N.Q and R.N.Q.; methodology, E.N.Q., L.A.I., G.A.M, E.D.A.,H.G.T, D.L.A., R.G.A, M.O.R., C. and L.G.E.; writing—original draft preparation, E.N.Q., R.N.Q., E.D.A., A.C.B., J.S.G., and C.C.G.,. All authors contributed to the study design and preparation of the manuscript and have read and approved the final version.

Funding: We declare that the funds or sources of support received in this specific internal report study were from Simón Bolívar University, Barranquilla, Colombia and that the external funding was from the Ministery of Science, Technology, and Innovation of Colombia, subsidy 125380763038 and 125380763188. We clarified that the funder had no role in the design of the study, in the collection and analysis of data, in the decision to publish, or in the preparation of the manuscript

Acknowledgments:

Simón Bolívar University and Ministery of Science, Technology, and Innovation of Colombia for facilitating the resources for article publication

Conflicts of Interest:

the authors state that they have no conflicts of interest

References

[1] M. A. Friedman *et al.*, "An Updated Review of Ciguatera Fish Poisoning: Clinical, Epidemiological, Environmental, and Public Health Management," *Mar. Drugs*, vol. 15, no. 3, Mar. 2017, doi: 10.3390/md15030072.

[2] A. Ruiz Gómez, J. E. Mancera Pineda, A. Ruiz Gómez, and J. E. Mancera Pineda, "POTENTIALLY TOXIC DINOFLAGELLATES ASSOCIATED TO SEAGRASS ON ISLA DE BARÚ, COLOMBIAN CARIBBEAN, DURING EL NIÑO 2015," *Acta Biológica Colomb.*, vol. 24, no. 1, pp. 109–117, Apr. 2019, doi: 10.15446/abc.v24n1.61799.

[3] P. J. Scheuer, W. Takahashi, J. Tsutsumi, and T. Yoshida, "Ciguatoxin: Isolation and Chemical Nature," *Science*, vol. 155, no. 3767, pp. 1267–1268, Mar. 1967, doi: 10.1126/science.155.3767.1267.

[4] M. Murata, A. M. Legrand, Y. Ishibashi, and T. Yasumoto, "Structures of ciguatoxin and its congener," *J. Am. Chem. Soc.*, vol. 111, no. 24, pp. 8929–8931, Nov. 1989, doi: 10.1021/ja00206a032.

[5] R. J. Lewis, J.-P. Vernoux, and I. M. Brereton, "Structure of Caribbean Ciguatoxin Isolated from Caranx latus," *J. Am. Chem. Soc.*, vol. 120, no. 24, pp. 5914–5920, Jun. 1998, doi: 10.1021/ja980389e.

[6] J. S. Celis and J. E. Mancera Pineda, "ANÁLISIS HISTÓRICO DE LA INCIDENCIA DE CIGUATERA EN LAS ISLAS DEL CARIBE DURANTE 31 AÑOS: 1980 – 2010," *Bull. Mar. Coast. Res.*, vol. 44, no. 1, Jan. 2016, doi: 10.25268/bimc.invemar.2015.44.1.18.

[7] R. Alvarez, "Primer caso de ciguatera en el caribe colombiano por Seriola zonata (Mitchill, 181 5) (Pisces: Carangidae)," *Biomédica*, vol. 17, no. 1, p. 67, Mar. 1997, doi: 10.7705/biomedica.v17i1.928.

[8] J. E. Mancera-Pineda, M. Montalvo-Talaigua, and B. Gavio, "Dinoflagelados potencialmente tóxicos asociados a material orgánico flotante (drift) en San Andrés Isla, Reserva Internacional de la Biosfera-Seaflower: potentially toxic dinoflagellates associated to drift in San Andrés Island, International Biosphere Reservation-Seaflower," *Caldasia*, vol. 36, no. 1, pp. 139–156, 2014.

[9] E. A. Rodriguez, J. E. Mancera Pineda, and B. Gavio, "SURVEY OF BENTHIC DINOFLAGELLATESASSOCIATED TO BEDS OF Thalassia testudinumIN SAN ANDRÉS ISLAND, SEAFLOWER BIOSPHERE RESERVE,CARIBBEAN COLOMBIA.," *Acta Biológica Colomb.*, vol. 15, no. 2, pp. 229–246, Aug. 2010, Accessed: Mar. 01, 2020. [Online]. Available: http://www.scielo.org.co/scielo.php?script=sci_abstract&pid=S0120-548X2010000200016&lng=en&nrm=iso&tlng=en.

[10] J. D. G. Espitia, "Ictiotoxismo por consumo de barracuda (Sphyraena barracuda) y morena manchada (Gymnothorax moringa) en la comunidad de pescadores artesanales de Tasajera, Caribe colombiano," *Duazary*, vol. 4, no. 2, Art. no. 2, 2007, doi: 10.21676/2389783X.656.

[11] B. Ramos and M. Edith, "Asociación entre la Temperatura Ambiental y Temperatura Superficial del Mar sobre la Aparición de Casos de Ciguatera en el Departamento de San Andrés y Providencia," Dec. 2015, Accessed: Mar. 07, 2020. [Online]. Available: http://repository.udistrital.edu.co/handle/11349/3738.

[12] S. R. Kibler, E. D. Davenport, P. A. Tester, D. R. Hardison, W. C. Holland, and R. W. Litaker, "Gambierdiscus and Fukuyoa species in the greater Caribbean: Regional growth projections for ciguatera-associated dinoflagellates," *Ecol. Model.*, vol. 360, pp. 204–218, Sep. 2017, doi: 10.1016/j.ecolmodel.2017.07.007.

[13] A. G. Uribe, M. L. O. Martínez, H. Quijada, and M. E. M. Durán, "Perfil epidemiológico de las intoxicaciones por sustancias químicas en Colombia," vol. 22, p. 24, 2013, [Online]. Available: http://repository.udistrital.edu.co/bitstream/11349/3738/1/MILENA%20BORBON.pdf.

[14] L. L. Rhodes, K. F. Smith, J. S. Murray, T. Nishimura, and S. C. Finch, "Ciguatera Fish Poisoning: The Risk from an Aotearoa/New Zealand Perspective," *Toxins*, vol. 12, no. 1, Art. no. 1, Jan. 2020, doi: 10.3390/toxins12010050.

[15] M. Yan *et al.*, "Effects of dietary exposure to ciguatoxin P-CTX-1 on the reproductive performance in marine medaka (Oryzias melastigma)," *Mar. Pollut. Bull.*, vol. 152, p. 110837, Mar. 2020, doi: 10.1016/j.marpolbul.2019.110837.

[16] L. Soliño and P. R. Costa, "Global impact of ciguatoxins and ciguatera fish poisoning on fish, fisheries and consumers," *Environ. Res.*, vol. 182, p. 109111, Mar. 2020, doi: 10.1016/j.envres.2020.109111.

[17] J. A. Sanchez-Henao *et al.*, "Predictive score and probability of CTX-like toxicity in fish samples from the official control of ciguatera in the Canary Islands," *Sci. Total Environ.*, vol. 673, pp. 576–584, Jul. 2019, doi: 10.1016/j.scitotenv.2019.03.445.

[18] L. Meyer, A. Capper, S. Carter, and C. Simpfendorfer, "An investigation into ciguatoxin bioaccumulation in sharks," *Toxicon Off. J. Int. Soc. Toxinology*, vol. 119, pp. 234–243, Sep. 2016, doi: 10.1016/j.toxicon.2016.06.007.

[19] V. F. Magalhães *et al.*, "Microcystins (cyanobacteria hepatotoxins) bioaccumulation in fish and crustaceans from Sepetiba Bay (Brasil, RJ)," *Toxicon*, vol. 42, no. 3, pp. 289–295, Sep. 2003, doi: 10.1016/S0041-0101(03)00144-2.

[20] D. A. Alavarado and J. M. R. Vera, "Dynamics of the bioaccumulation of ciguatoxins in a food chain," *Rev. Cuba. Investig. Bioméd.*, vol. 32, no. 3, pp. 271–283, 2013, Accessed: Mar. 07, 2020. [Online]. Available: https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDARTICULO=48504.

[21] N. A. Palafox and L. E. Buenconsejo-Lum, "CIGUATERA FISH POISONING: REVIEW OF CLINICAL MANIFESTATIONS," *J. Toxicol. Toxin Rev.*, vol. 20, no. 2, pp. 141–160, Jan. 2001, doi: 10.1081/TXR-100105733.

[22] "Clinical Observations on 3,009 Cases of Ciguatera (Fish Poisoning) in the South Pacific - PubMed." https://pubmed.ncbi.nlm.nih.gov/574366/ (accessed Jun. 15, 2020).

[23] M. P. Skinner, T. D. Brewer, R. Johnstone, L. E. Fleming, and R. J. Lewis, "Ciguatera Fish Poisoning in the Pacific Islands (1998 to 2008)," *PLoS Negl. Trop. Dis.*, vol. 5, no. 12, Dec. 2011, doi: 10.1371/journal.pntd.0001416.

[24] D. N. Lawrence, "Ciguatera Fish Poisoning in Miami," *JAMA J. Am. Med. Assoc.*, vol. 244, no. 3, p. 254, Jul. 1980, doi: 10.1001/jama.1980.03310030030021.

[25] J. K. Sims, "A theoretical discourse on the pharmacology of toxic marine ingestions," *Ann. Emerg. Med.*, vol. 16, no. 9, pp. 1006–1015, Sep. 1987, doi: 10.1016/S0196-0644(87)80750-3.

[26] A. Edwards, A. Zammit, and H. Farrell, "Four recent ciguatera fish poisoning incidents in New South Wales, Australia linked to imported fish," *Commun. Dis. Intell.*, vol. 43, Feb. 2019, doi: 10.33321/cdi.2019.43.4.

[27] M. Friedemann, "Ciguatera fish poisoning outbreaks from 2012 to 2017 in Germany caused by snappers from India, Indonesia, and Vietnam," *J. Consum. Prot. Food Saf.*, vol. 14, no. 1, pp. 71–80, Mar. 2019, doi: 10.1007/s00003-018-1191-8.

[28] C. K. Neves Junior, L. Z. Goldani, C. K. Neves Junior, and L. Z. Goldani, "Ciguatera fish poisoning in Brazilian traveler to Caribbean," *Braz. J. Infect. Dis.*, vol. 23, no. 3, pp. 200–202, Jun. 2019, doi: 10.1016/j.bjid.2019.06.004.

[29] M. J. Ortega Chavarría, D. Alcocer Delgado, E. J. Diaz Greene, and F. L. Rodríguez Weber, "Ciguatera poisoning: infectious cause neuropathy," *Acta Médica Grupo Ángeles*, vol. 17, no. 3, pp. 268–271, 2019, Accessed: Mar. 08, 2020. [Online]. Available: https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDREVISTA=32&IDARTICULO=89088&IDPUBLICACION=8467.

[30] R. Raman, S. Coppes, T. Hellingman, and C. Laclé, "Junctional bradycardia caused by ciguatera intoxication," *BMJ Case Rep.*, vol. 12, no. 5, p. e229354, May 2019, doi: 10.1136/bcr-2019-229354.

[31] M. Chinain, C. M. Gatti, M. Roué, and H. T. Darius, "Ciguatera poisoning in French Polynesia: insights into the novel trends of an ancient disease," *New Microbes New Infect.*, vol. 31, Jun. 2019, doi: 10.1016/j.nmni.2019.100565.

[32] G. Asaeda, "The transport of ciguatoxin: A case report11Selected Topics: Toxicology is coordinated by Kenneth Kulig, MD, of Denver, Colorado," *J. Emerg. Med.*, vol. 20, no. 3, pp. 263–265, Apr. 2001, doi: 10.1016/S0736-4679(00)00319-X.

[33] H. Farrell *et al.*, "Clinical diagnosis and chemical confirmation of ciguatera fish poisoning in New South Wales, Australia," *Commun. Dis. Intell. Q. Rep.*, vol. 40, no. 1, pp. E1-6, Mar. 2016.

[34] M. V. Milaciu, L. Ciumărnean, O. H. Orășan, I. Para, T. Alexescu, and V. Negrean, "Semiology of food poisoning.," *HVM Bioflux*, vol. 8, no. 2, pp. 108–113, 2016, Accessed: Mar. 08, 2020. [Online]. Available: https://www.cabdirect.org/cabdirect/abstract/20163245080.

[35] A. Caillaud *et al.*, "Update on Methodologies Available for Ciguatoxin Determination: Perspectives to Confront the Onset of Ciguatera Fish Poisoning in Europe []," *Mar. Drugs*, vol. 8, no. 6, pp. 1838–1907, Jun. 2010, doi: 10.3390/md8061838.

[36] M. Bodero *et al.*, "A Strategy to Replace the Mouse Bioassay for Detecting and Identifying Lipophilic Marine Biotoxins by Combining the Neuro-2a Bioassay and LC-MS/MS Analysis," *Mar. Drugs*, vol. 16, no. 12, Dec. 2018, doi: 10.3390/md16120501.

[37] A. Humpage, V. Magalhaes, and S. Froscio, "Comparison of analytical tools and biological assays for detection of paralytic shellfish poisoning toxins," *Anal. Bioanal. Chem.*, vol. 397, no. 5, pp. 1655–1671, 2010.

[38] R.-E. B and B. Y, "Rabbitfish ('aras'): an unusual source of ciguatera poisoning.," *Isr. Med. Assoc. J. Imaj*, vol. 4, no. 1, pp. 28–30, Jan. 2002, Accessed: Mar. 08, 2020. [Online]. Available: https://europepmc.org/article/med/11802305.

[39] A. Saraya *et al.*, "Marine Fish Toxins in Thailand: Report of 6 Suspected Ciguatera Cases," *Case Rep. Clin. Med.*, vol. 2014, May 2014, doi: 10.4236/crcm.2014.35065.

[40] V. Álvarez Rivero, R. Cervantes Zorrilla, M. Lorea Cárdenas-Hernández, and M. A. González-Chávez, "Scombroidosis," *Acta Médica Grupo Ángeles*, vol. 16, no. 1, pp. 63–65, Mar. 2018, Accessed: Mar. 08, 2020. [Online]. Available: https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDREVISTA=32&IDARTICULO=77664&IDPUBLICACION=7517.

[41] N. C. Gillespie *et al.*, "Ciguatera in Australia: Occurrence, clinical features, pathophysiology and management," *Med. J. Aust.*, vol. 145, no. 11–12, pp. 584–590, 1986, doi: 10.5694/j.1326-5377.1986.tb139504.x.

[42] M. A. Friedman *et al.*, "Ciguatera Fish Poisoning: Treatment, Prevention and Management," *Mar. Drugs*, vol. 6, no. 3, Art. no. 3, Sep. 2008, doi: 10.3390/md6030456.

[43] N. A. Palafox, L. G. Jain, A. Z. Pinano, T. M. Gulick, R. K. Williams, and I. J. Schatz, "Successful Treatment of Ciguatera Fish Poisoning With Intravenous Mannitol," *JAMA*, vol. 259, no. 18, pp. 2740–2742, May 1988, doi: 10.1001/jama.1988.03720180066035.

[44] G. Bourdy, P. Cabalion, P. Amade, and D. Laurent, "Traditional remedies used in the Western Pacific for the treatment of ciguatera poisoning," *J. Ethnopharmacol.*, vol. 36, no. 2, pp. 163–174, Apr. 1992, doi: 10.1016/0378-8741(92)90017-L.

[45] T. Y. K. Chan, "Severe bradycardia and prolonged hypotension in ciguatera," *Singapore Med. J.*, vol. 54, no. 6, pp. e120-122, Jun. 2013, doi: 10.11622/smedj.2013095.

[46] M.-L. Chateau-Degat *et al.*, "Prevalence of Chronic Symptoms of Ciguatera Disease in French Polynesian Adults," *Am. J. Trop. Med. Hyg.*, vol. 77, no. 5, pp. 842–846, Nov. 2007, doi: 10.4269/ajtmh.2007.77.842.