Ciguatera poisoning in French Polynesia: insights into the novel trends of an ancient disease

M. Chinain[1], C. M. Gatti[1], M. Roué[2] and H. T. Darius[1]

1) *Institut Louis Malardé, Laboratory of Marine Biotoxins—UMR 241-EIO, Papeete, Tahiti, French Polynesia* and 2) *Institut de Recherche pour le Développement—UMR 241-EIO, Pirae, Tahiti, French Polynesia*

Abstract

Ciguatera is a non-bacterial seafood poisoning highly prevalent in French Polynesia where it constitutes a major health issue and a major threat to food sustainability and food security for local populations. Ciguatera results from the bioaccumulation in marine food webs of toxins known as ciguatoxins, originating from benthic dinoflagellates in the genera *Gambierdiscus* and *Fukuyoa*. Ciguatera is characterized by a complex array of gastrointestinal, neurological and cardiovascular symptoms. The effective management of patients is significantly hampered by the occurrence of atypical forms and/or chronic sequelae in some patients, and the lack of both a confirmatory diagnosis test and a specific antidote. In addition, recent findings have outlined the implication of novel species of the causative organisms as well as new vectors, namely marine invertebrates, in ciguatera outbreaks. Another novel trend relates to the geographical expansion of this disease to previously unaffected areas, not only in certain island groups of French Polynesia but also in temperate regions worldwide, as a likely consequence of the effects of climate change.
© 2019 The Authors. Published by Elsevier Ltd.

Corresponding author: M. Chinain, Institut Louis Malardé (ILM), Laboratory of Marine Biotoxins—UMR 241-EIO, PO Box 30, Papeete 98713, Tahiti, *French Polynesia*.
E-mail: mchinain@ilm.pf

Fish products represent a major subsistence resource for French Polynesia populations whose per-capita fish consumption may exceed 100 kg/year in some islands [1]. This heavy reliance on a fish-based diet makes local communities particularly vulnerable to seafood-related poisonings. Among the six poisoning syndromes reported in French Polynesia, including tetrodotoxism (puffer fish), chelonitoxism (turtle), clupeotoxism (clupeids), carchatoxism (sharks) and paralytic shellfish poisoning (crabs) [2,3], ciguatera constitutes the most prevalent form of poisoning, as evidenced by the high incidence rates consistently reported from most of the island groups in French Polynesia (Table 1). Although ciguatera is not a new disease *per se*—early accounts of poisoning incidents are found in Captain

James Cook's journal in 1774—significant research progress achieved in the last decade has led to a reconsideration of several of the early paradigms in ciguatera pertaining to, for example, the causative organisms, the vectors involved in ciguatera transmission pathways, and the biogeographical range of this disease.

Clinical manifestations of ciguatera

Ciguatera is characterized by a complex set of polymorphic and non-specific symptoms, resulting from the diversity of the biological targets of ciguatoxins (CTXs) (e.g. voltage-gated sodium and potassium channels) and the negative impacts of CTXs on nerve transmission [4]. These symptoms vary from individual to individual, and also depend on the amount of toxins ingested as well as the geographic origin of the consumed fish: overall, 175 symptoms have been reported in the literature [5], making ciguatera diagnosis particularly challenging, especially in non-endemic regions. Of note, ciguatera does not seem

to confer any immunity in its victim but often results in increased sensitivity to marine products.

In the absence of confirmatory clinical tests, ciguatera diagnosis is based exclusively on the patient's history, case clusters, suggestive clinical manifestations and differential diagnosis. Ciguatera must be evoked in a non-febrile patient presenting with a combination of gastrointestinal, cardiovascular and neurological disorders [6] in the absence of allergic reactions, developed within 48 hours following the consumption of marine products from tropical/subtropical regions reputed as ciguatera hotspots. Classically, individuals with ciguatera in French Polynesia first suffer from diarrhoea and/or vomiting, possibly associated with a transient hypothermia and cardiovascular symptoms, mostly bradycardia and hypotension (tachycardia and hypertension described to a lesser extent), which may be considered as a criterion of severity [7]. In some instances—for example, poisoning cases following the ingestion of toxic marine invertebrates—atypical symptoms may be observed such as the rapid onset of the disease (within minutes, in some reported cases), and the unusual severity of symptoms including paralysis that sometimes requires the patients' hospitalization [8,9], suggesting that other toxins may potentially be involved in these atypical poisonings. Of note, in exceptionally severe forms, ciguatera can lead to Guillain–Barré syndrome and related neurological disorders [10].

In any case, these initial manifestations usually resolve within a few days giving place to a panel of neurological signs that include extremities/perioral paraesthesia, dysaesthesia (mostly allodynia in response to cold stimuli), muscle weakness, dizziness, headache, visual/balance/concentration and sleep disorders, associated with a pruritus (without cutaneous signs), asthenia, myalgia, arthralgia, oropharyngeal burning, dysgeusia, orofacial pain, and sometimes urogenital discomfort/burning (Table 2). The high predominance of neurological signs in French Polynesian patients is similar to what is observed in the Indian Ocean, except that neuropsychiatric component, such as hallucinations [11], has little been reported in French Polynesia. In all cases, these clinical manifestations spontaneously regress within a few weeks in most patients, however, up to 20% of patients are likely to develop chronic sequelae involving dysaesthesia, paraesthesia, asthenia, general malaise, cognitive/mood disorders and chronic fatigue evocative syndrome, which may persist for months or even years [6,12,13]. Chronic symptoms can express continuously or by short-term peaks, are revived by triggering factors such as food and drinks (marine-related products, meats, foods rich in histamine and protein, nuts), drinks (alcohol, high-energy drinks) and specific circumstances (intense physical activity, cold/hot stimuli, stress) [6]. In most cases, these chronic manifestations eventually resolve in patients with ciguatera, but adopting an eviction diet may help patients to recover more quickly. Regarding ciguatera treatment, the lack of specific and effective antidotes prompts case-by-case symptomatic medical support, although some studies have shown that intravenous mannitol may prove efficient if administered no later than 72 hours post-poisoning [14]. As for chronic symptoms, the biological mechanisms underlying these manifestations are still poorly documented and effective medical solutions are yet to be identified [15]. Of note, many South Pacific communities use traditional remedies, most notably a leaf decoction of the octopus bush *Heliotropium foetherianum*, arguably with great success [16].

Ciguatera causative organisms and related toxins: identification of novel species and toxic compounds

The mode of transmission of ciguatera to humans is well documented: ciguatera results from the consumption of marine products contaminated by sufficiently high concentrations of lipophilic compounds, CTXs. These toxins are produced by a

TABLE 1. Annual incidence rate of ciguatera poisoning cases reported in French Polynesia from 2007 to 2017[a]

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Archipelagos											
Society	3	6	6	7	9	6	4	2	1	3	3
Marquesas	66	125	105	74	87	89	55	50	30	53	87
Tuamotu	121	134	106	104	92	101	60	37	60	220	63
Gambier	539	516	531	591	307	338	77	70	169	345	—[b]
Australes	65	79	236	170	55	47	89	28	72	39	46
Rapa island	0	124	1826	892	270	330	660	194	291	233	0
Animal consumed											
Trochus	0	0	0	0	0	0	0	2 (10)	0	0	0
Sea urchin	0	0	2 (7)	1 (2)	0	0	1 (2)	0	2 (3)	0	0
Giant clam	0	1 (1)	1 (1)	1 (1)	0	0	1 (1)	0	0	0	1(1)

Incidence rate expressed in number of cases/10 000 inhabitants). These statistics do not take into account the under-reporting rate, estimated at 31% for the same period. The number of ciguatera-like poisoning events due to consumption of trochus (*Tectus niloticus*), sea urchins (*Tripneustes gratilla*) and giant clams (*Tridacna maxima*) for the same period are also indicated with the number of persons concerned (in italics and in brackets).
[a]Data source: Bureau de Veille Sanitaire, Public Health Directorate of French Polynesia—Institut Louis Malardé (www.ciguatera.pf).
[b]—, no report available for 2017.

benthic dinoflagellate, *Gambierdiscus* spp., and are readily transferred through marine food webs, from algae to herbivorous then carnivorous fish, by grazing and predation respectively, and ultimately to humans. Natural and anthropogenic disturbances are some of the factors likely to exacerbate ciguatera risk in coral reef environments [17] (Fig. 1).

Until 1999, only a limited number of species (six species) were known in the genus *Gambierdiscus* [18,19]. Since 2009, however, the use of genetic data combined with morphological data has dramatically accelerated the detection of multiple novel species, and more species are likely to be discovered in the next few years. Currently the genus *Gambierdiscus* comprises 15 described species plus several ribotypes ([20−22] and references therein) and three sister species in the new genus *Fukuyoa* [23]. Based on the existing literature, most species found in the Pacific are distinct from those in the Atlantic region, although some species clearly show a marked cosmopolitan distribution [24,25]. Field data obtained from risk assessment campaigns indicate that at least six of the described species are present in French Polynesia, namely *Gambierdiscus toxicus*, *Gambierdiscus australes*, *Gambierdiscus pacificus*, *Gambierdiscus polynesiensis*, *Gambierdiscus caribaeus* and *Gambierdiscus carpenteri* [26,27]. To the best of our knowledge, specimens of the genus *Fukuyoa* have not been reported from French Polynesian waters.

Besides CTXs, *Gambierdiscus* also produces several other toxic compounds (e.g. maitotoxins, gambieric acids, gambierol, gambieroxide, and gambierone) [28,29] and references therein), and as significant progress has been achieved in detection techniques, novel compounds are likely to be found in this genus, as exemplified by the recent characterization of a novel maitotoxin compound [30]. However, the ecological relevance of these compounds (e.g. as allelopathic agents) remains elusive, and their potential contribution to ciguatera syndrome still needs to be clarified.

The ability to produce CTXs seems to be genetically determined in the *Gambierdiscus/Fukuyoa* complex and reports of the existence of clonal variations ranging from toxic to non-ciguatoxic cells are available in the literature [31,32]. The
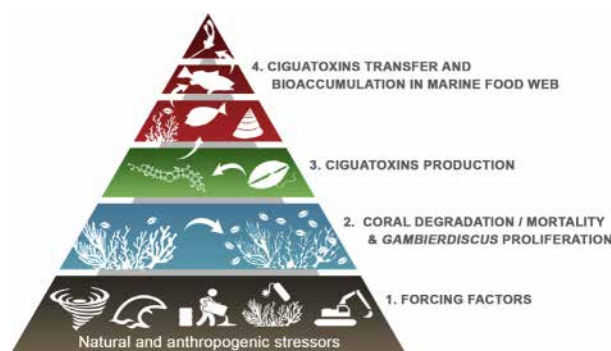

FIG. 1. The trophic chain of ciguatera poisoning.

species- and strain-dependent production of CTXs explains that the presence of *Gambierdiscus* alone in a given area does not necessarily imply a proven poisoning risk, which depends in part on the strains' toxic potential and hence the level of CTXs actually introduced in the marine food web. In terms of risk-forecasting implications, only two species, *G. polynesiensis* and *Gambierdiscus excentricus*, are known to produce substantial amounts of CTXs [31−33], suggesting their potential use as biomarkers of high ciguatera risk in areas colonized by *Gambierdiscus* populations.

Ciguatera transmission pathways: implication of novel vectors in French Polynesia

Ciguatera classically results from the ingestion of tropical and subtropical coral reef fish. However, a variety of marine invertebrates that also represent a valuable source of protein and revenue for Pacific island communities, are episodically involved in ciguatera-like poisoning incidents (Fig. 2). The first ever report concerns the giant clam *Tridacna maxima*, which was implicated in a mass-poisoning event in 1964 in Bora Bora Island (Society archipelago) leading to two fatalities [34], and in 2005 in Raivavae Island (Australes) [8]. Of note, a recent study has

TABLE 2. Prevalence of ciguatera clinical symptoms based on the analysis of 727 declaration forms (ambulatory cases) registered between 2014 and 2017[a] in French Polynesia

| Digestive | Cardiovascular | Neurological | | Other |
		Peripheral	Central	
Diarrhoea (75%)	Bradycardia (22%)	Paraesthesia (80%)	Dizziness (52%)	Arthralgia (61%)
Nausea (44%)	Hypotension (17%)	Cold allodynia (71%)	Headache/migraine (52%)	Pruritus/itching (49%)
Vomiting (37%)		Muscle disturbances (67%)	Transient hypothermia (37%)	Dysgeusia (42%)
		Dysaesthesia (63%)	Visual disorder (18%)	Asthenia (26%)
				Urogenital discomfort/pain (17%)

[a]Data source: Bureau de Veille Sanitaire, Public Health Directorate of French Polynesia—Institut Louis Malardé (www.ciguatera.pf).
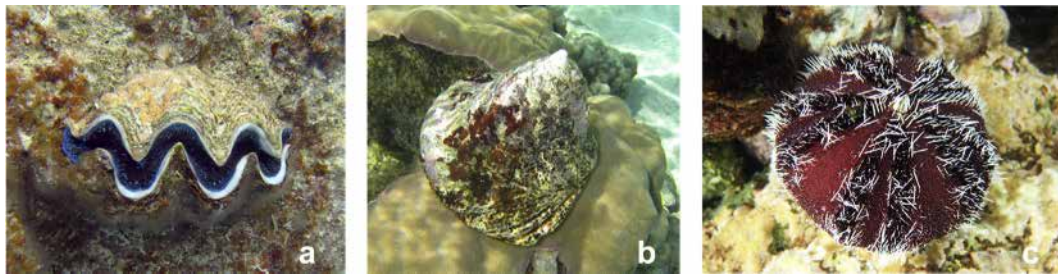
FIG. 2. Marine invertebrates are also susceptible to bioaccumulate ciguatoxins. A) the giant clam *Tridacna maxima* (Tridacnidae, Bivalvia), B) the trochus *Tectus niloticus* (Tegulidae, Gastropoda) and C) the sea urchin *Tripneustes gratilla* (Toxopneustidae, Echinoidea).

provided evidence for the bioaccumulation of CTXs in *Tridacna maxima* experimentally exposed to *Gambierdiscus* cells [35,36]. Toxic incidents following the ingestion of *Tripneustes gratilla* (sea urchin) and *Tectus niloticus* (gastropod) have been documented from Rurutu Island (Australes) and, more recently, from Nuku Hiva Island (Marquesas) [9,26,27,37]. Coincidentally, the affected area in Nuku Hiva Island was also the one with high *Gambierdiscus* densities and high prevalence of toxic fish. At a regional scale, sporadic poisoning cases involving *Tridacna maxima*, *Octopus cyanea* (big blue octopus), *Percnon* spp. (nimble spray crab) and *Dendropoma maxima* (large worm shell) have been reported from the Cook Islands [38], as well as *Panulirus penicillatus* (lobster) and octopus from the Republic of Kiribati [39]. Outside the Pacific region, *Tripneustes esculentus* (sea urchin) has been incriminated in toxic events in the West Indies [40], while two starfish from waters off Madeira, *Ophidiaster ophidianus* and *Marthasterias glacialis*, have been found also to bioaccumulate CTXs [41].

Toxicological analysis using the neuroblastoma cell-based assay and liquid chromatography-tandem mass spectrometry were further performed on *Tectus niloticus* and *Tripneustes gratilla* toxic samples collected from Anaho Bay, a long-standing ciguatera hotspot from Nuku Hiva Island (Marquesas) (http://www.ciguatera.pf/index.php/fr/cartographie-dynamique). They allowed for the unambiguous detection of CTX compounds in these samples [26,27] at levels consistently above the US Food and Drug Administration advisory levels (0.01 equiv P-CTX1 ng.g^{-1}) [42]. Based on liquid chromatography-tandem mass spectrometry data, at least five distinct CTX congeners could be detected [26,27], some of which are known to be primarily produced by *G. polynesiensis* in *in vitro* cultures [31]. Interestingly, some of these compounds also corresponded to the CTXs mainly detected in *Tridacna maxima* experimentally fed highly toxic cells of *G. polynesiensis* [35,36]. All these findings, which are consistent with the observation that *G. polynesiensis* is actually the dominant species in Anaho Bay [26,27], suggest that *Gambierdiscus* is the likely source of the CTX compounds that are naturally bio-accumulated in a variety of marine invertebrates.

Considering that most ciguatera mitigation programmes currently rely solely on the survey of *Gambierdiscus* populations and/or the monitoring of CTXs in fish, these data highlight the importance of also extending such surveys to several species of marine invertebrates that are highly prized by local populations, as they actually represent a potential risk for human consumption.

Geographical range of ciguatera: recent expansion to new areas

Another striking feature of ciguatera is its recent expansion to previously unaffected regions [43−45]. Globally, the endemic regions can be superimposed on coral development areas of the Caribbean Sea, and Pacific and Indian Oceans—that is, tropical and sub-tropical areas at low latitudes (between 35°N and 35°S) where the climatology and water conditions are more favourable to the development of *Gambierdiscus* spp. [25]. Rapa Island is located in the southernmost part of the Australes archipelago in French Polynesia, at latitudes near those of temperate locations, and was reputed to be completely free of ciguatera until 2008 when the first cases emerged (Table 1). In 2009, a mass-poisoning event affected half the population following a community fishing party. Clinical records indicated symptoms similar to ciguatera in affected individuals. The unusual severity and magnitude of this outbreak led to two fatalities. Field investigations allowed for the detection of toxic *Gambierdiscus* populations in several sampling sites of Rapa Island, and the presence of CTXs in herbivorous and carnivorous fish at concentrations well above the guidance level [37], confirming the emergence of a novel ciguatera-prone area in French Polynesia. Fortunately, the local population was highly reactive to educational and community outreach interventions, with a significant reduction in incidence rates (Table 1); a result attributable to self-regulating behaviour among the population [19].

More broadly, the case of Rapa Island is emblematic of the current expansion of *Gambierdiscus* spp. and ciguatoxic fish to

previously ciguatera-naive regions, most notably to temperate areas, as is the case for several locations in the eastern Atlantic Ocean (Madeira and Canary Islands) where endogenous cases have been reported since 2004 [44,45]. These observations are consistent with the detection of *Gambierdiscus* spp. (including two novel species) in Macaronesian waters, and the confirmation of CTX contamination in indigenous fish [46,47]. Since this date, reports of *Gambierdiscus* spp. and *Fukuyoa* spp. populations are being continually documented from other regions of the globe, such as the Gulf of Mexico, the Mediterranean Sea, Northland New Zealand, Pakistan, the Arabian Gulf and the Red Sea, ([21] and references therein). As a result, our concept of what habitats are suitable for *Gambierdiscus* spp. (e.g. temperature, irradiance, or depth range) is also likely to change [48].

Owing to the high incidence rates reported annually from French Polynesia, ciguatera is not only a major public health issue but also represents a major threat to food sustainability and food security of local communities. Even more alarming, this issue is expected to increase in the context of global change and increased eutrophication in coral reef environments [49], stressing the urgent need for accelerating the implementation of ciguatera mitigation programmes at a global scale. A first significant step towards this goal is the recent request filed by the Codex Committee on Contaminants in Food (www. codexalimentarius.org) to the Food and Agriculture Organization of the United Nations/World Health Organization for scientific advice on the maximum limits for CTXs and for risk management guidelines (http://www.fao.org/fao-who-codexalimentarius/news-and-events/news-details/fr/c/1173604/).

Authors' contribution

MC, CMG, MR and HTD have drafted the article, revised it and approved the final version to be submitted.

Transparency declaration

The authors declare no conflicts of interest.

References

[1] Seguin F. La pêche. In: Seguin F, editor. Etat de l'environnement en Polynésie française 2007/2014. Tahiti, Polynésie française: Direction de l'Environnement, Creocean, Ministère de l'environnement, de l'énergie et des mines direction de l'environnement; 2015. p. 258–63. https://docplayer.fr/24663888-La-peche-la-perliculture-et-l-aquaculture.html.

[2] Gatti C, Oelher E, Legrand AM. Severe seafood poisoning in French Polynesia: a retrospective analysis of 129 medical files. Toxicon 2008;51:746–53.

[3] Chinain M. Les maladies liées aux toxines marines. In: Seguin F, editor. Etat de l'Environnement en Polynésie française 2007/2014. Tahiti, Polynésie française: Direction de l'Environnement, Creocean, Ministère de l'environnement, de l'énergie et des mines direction de l'environnement; 2015. p. 198–202.

[4] Mattei C, Benoit E, Molgó J. An overview of the ion channel modulation and neurocellular disorders induced by ciguatoxins. Toxins and Ion transfers, Collection Rencontres en Toxinologie. Gif-sur-Yvette France: SFET Publications; 2011. p. 39–42. https://hal.archives-ouvertes.fr/hal-00738586.

[5] Sims JK. A theoretical discourse on the pharmacology of toxic marine ingestions. Ann Emerg Med 1987;16:1006–15.

[6] Friedman M, Fernandez M, Backer L, Dickey R, Bernstein J, Schrank K, et al. An updated review of ciguatera fish poisoning: clinical, epidemiological, environmental, and public health management. Mar Drugs 2017;15:72.

[7] Pearn J. Neurology of ciguatera. J Neurol Neurosurg Psychiatr 2001;70:4–8.

[8] Laurent D, Kerbrat AS, Darius HT, Rossi F, Yeeting B, Haddad M, et al. Ciguatera shellfish poisoning (CSP): a new ecotoxicological phenomenon from cyanobacteria to humans via giant clams. In: Jensen MA, et al., editors. Food chains: new research. New York: Nova Science Publishers, Inc.; 2012. p. 1–43. Chapter 1.

[9] Gatti CM, Lonati D, Darius HT, Zancan A, Roué M, Amzil Z, et al. *Tectus niloticus* (Tegulidae, Gastropod), as a novel vector of ciguatera poisoning. Clinical characterization and follow up of a mass poisoning event in Nuku Hiva Island (Marquesas archipelago, French Polynesia). Toxins 2018;10:102.

[10] Oehler E, Gatti C, Legrand AM, Ghawche F. [Ciguatera and acute polyradiculoneuritis. Description of two cases in French Polynesia: immunoallergic hypothesis?]. Med Trop (Mars) 2009;69:75–7.

[11] Quod JP, Turquet J. Ciguatera in Réunion Island (SW Indian Ocean): epidemiology and clinical patterns. Toxicon 1996;34:779–85.

[12] Baumann F, Bourrat MB, Pauillac S. Prevalence, symptoms and chronicity of ciguatera in New Caledonia: results from an adult population survey conducted in Noumea during 2005. Toxicon 2010;56:662–7.

[13] Pearn J. Chronic ciguatera. J Chron Fatigue Syndr 1996;2:29–34.

[14] Bagnis R, Spiegel A, Boutin JP, Burucoa C, Nguyen L, Cartel JL, et al. [Evaluation of the efficacy of mannitol in the treatment of ciguatera in French Polynesia]. Med Trop (Mars) 1992;52:67–73.

[15] Mullins ME, Hoffman RS. Is mannitol the treatment of choice for patients with ciguatera fish poisoning? Clin Toxicol (Phila) 2017;55:947–55.

[16] Kumar-Roine S, Darius HT, Matsui M, Fabre N, Haddad M, Chinain M, et al. A review of traditional remedies of ciguatera fish poisoning in the Pacific. Phytother Res 2011;25:947–58.

[17] Chinain M, Darius HT, Ung A, Tchou Fouc M, Revel T, Cruchet P, et al. Ciguatera risk management in French Polynesia: the case study of Raivavae Island (Australes archipelago). Toxicon 2010;56:674–90.

[18] Adachi R, Fukuyo Y. The thecal structure of a toxic marine dinoflagellate *Gambierdiscus toxicus* gen. et spec. nov. collected in a ciguatera-endemic area. Bull Jap Soc Sci Fish 1979;45:67–71.

[19] Chinain M, Faust MA, Pauillac S. Morphology and molecular analyses of three toxic species of *Gambierdiscus* (Dinophyceae): *G. pacificus*, sp. nov., *G. australes*, sp. nov., and *G. polynesiensis*, sp. nov. J Phycol 1999;35:1282–96.

[20] Litaker RW, Vandersea MW, Faust MA, Kibler SR, Chinain M, Holmes MJ, et al. Taxonomy of *Gambierdiscus* including four new species, *Gambierdiscus caribaeus*, *Gambierdiscus carolinianus*, *Gambierdiscus carpenteri* and *Gambierdiscus ruetzleri* (Gonyaulacales, Dinophyceae). Phycologia 2009;48:344–90.

[21] Lyu Y, Richlen ML, Sehein TR, Chinain M, Adachi M, Nishimura T, et al. LSU rDNA based RFLP assays for the routine identification of *Gambierdiscus* species. Harmful Algae 2017;66:20−8.

[22] Rhodes L, Smith KF, Verma A, Curley BG, Harwood DT, Murray S, et al. A new species of *Gambierdiscus* (Dinophyceae) from the south-west Pacific: *Gambierdiscus honu* sp. nov. Harmful Algae 2017;65:61−70.

[23] Gomez F, Qiu D, Lopes RM, Lin S. *Fukuoya paulensis* gen. et sp. nov., a new genus for the globular species of the dinoflagellate *Gambierdiscus* (Dinophyceae). PLoS One 2015;10:e0119676.

[24] Litaker RW, Vandersea MW, Faust MA, Kibler SR, Nau AW, Holland WC, et al. Global distribution of ciguatera causing dinoflagellates in the genus *Gambierdiscus*. Toxicon 2010;56:711−30.

[25] Parsons ML, Aligizaki K, Bottein M-YD, Fraga S, Morton SL, Penna A, et al. *Gambierdiscus* and *Ostreopsis*: reassessment of the state of knowledge of their taxonomy, geography, ecophysiology, and toxicology. Harmful Algae 2012;14:107−29.

[26] Darius HT, Roué M, Sibat M, Viallon J, Gatti C, Vandersea M, et al. *Tectus niloticus* (Tegulidae, Gastropod) as a novel vector of ciguatera poisoning: detection of Pacific ciguatoxins in toxic samples from Nuku Hiva Island (French Polynesia). Toxins 2018;10(1):2.

[27] Darius HT, Roué M, Sibat M, Viallon J, Gatti C, Vandersea M, et al. Toxicological investigations on the sea urchin *Tripneustes gratilla* (Toxopneustidae, Echinoid) from Anaho Bay (Nuku Hiva, French Polynesia): evidence for the presence of Pacific ciguatoxins. Marine Drugs 2018;16:122.

[28] Watanabe R, Uchida H, Suzuki T, Matsushima R, Nagae M, Toyohara Y, et al. Gambieroxide, a novel epoxy polyether compound from the dinoflagellate *Gambierdiscus toxicus* GTP2 strain. Tetrahedron 2013;69:10299−303.

[29] Rodríguez I, Genta-Jouve G, Alfonso C, Calabro K, Alonso E, Sánchez JA, et al. Gambierone, a ladder-shaped polyether from the Dinoflagellate *Gambierdiscus belizeanus*. Org Lett 2015;17:2392−5.

[30] Pisapia F, Sibat M, Herrenknecht C, Lhaute K, Gaiani G, Ferron P-J, et al. Maitotoxin-4, a novel MTX analog produced by *Gambierdiscus excentricus*. Marine Drugs 2017;15:220.

[31] Chinain M, Darius HT, Ung A, Cruchet P, Wang Z, Ponton D, et al. Growth and toxin production in the ciguatera-causing dinoflagellate *Gambierdiscus polynesiensis* (Dinophyceae) in culture. Toxicon 2010;56:739−50.

[32] Litaker RW, Holland WC, Hardison DR, Pisapia F, Hess P, Kibler SR, et al. Ciguatoxicity of *Gambierdiscus* and *Fukuoya* species from the Caribbean and Gulf of Mexico. PLoS ONE 2017;12:e0185776.

[33] Pisapia F, Holland WC, Hardison DR, Litaker RW, Fraga S, Nishimura T, et al. Toxicity screening of 13 *Gambierdiscus* strains using neuro-2a and erythrocyte lysis bioassays. Harmful Algae 2017;63:173−83.

[34] Bagnis R. A propos de quelques cas d'intoxications par des mollusques du genre "bénitier" dans une île de la Société. Bull Soc Pathol Exot 1967;60:580−92.

[35] Roué M, Darius HT, Picot S, Ung A, Viallon J, Gaertner-Mazouni N, et al. Evidence of the bioaccumulation of ciguatoxins in giant clams (*Tridacna maxima*) exposed to *Gambierdiscus* spp. cells. Harmful Algae 2016;57:78−87.

[36] Roué M, Darius H, Ung A, Viallon J, Sibat M, Hess P, et al. Tissue distribution and elimination of ciguatoxins in *Tridacna maxima* (Tridacnidae, Bivalvia) fed *Gambierdiscus polynesiensis*. Toxins 2018;10:189.

[37] Pawlowiez R, Darius HT, Cruchet P, Rossi F, Caillaud A, Laurent D, et al. Evaluation of seafood toxicity in the Australes archipelago (French Polynesia) using the neuroblastoma cell-based assay. Food Additives & Contaminants: A 2013;30:567−86.

[38] Rongo T, van Woesik R. Ciguatera poisoning in Rarotonga, southern Cook Islands. Harmful Algae 2011;10:345−55.

[39] Mak YL, Wai T-C, Murphy MB, Chan WH, Wu JJ, Lam JCW, et al. Pacific ciguatoxins in food web components of coral reef systems in the Republic of Kiribati. Environ Sci Technol 2013;47:14070−9.

[40] Earle KV. Pathological effects of two west Indian echinoderms. Trans R Soc Trop Med Hyg 1980;XXXIII:447−52.

[41] Silva M, Rodriguez I, Barreiro A, Kaufmann M, Neto AI, Hassouani M, et al. First Report of ciguatoxins in two starfish species: *Ophidiaster ophidianus* and *Marthasterias glacialis*. Toxins 2015;7:3740−57.

[42] Food and Drug Administration (FDA). Fish and fishery products hazards and control guidance. 2011. Available from: https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/seafood/ucm2018426.htm.

[43] Bienfang P, Oben B, DeFelice S, Moeller P, Huncik K, Oben P, et al. Ciguatera : the detection of neurotoxins in carnivorous reef fish from the coast of Cameroon, West Africa. Afr J Marine Sci 2008;30:533−40.

[44] Bravo J, Suarez FC, Ramirez AS, Acosta F. Ciguatera, an emerging human poisoning in Europe. J Aquacult Marine Biol 2015;3:00053.

[45] Perez-Arellano JL, Luzardo OP, Perez Brito A, Hernandez Cabrera M, Zumbado M, Carranza C, et al. Ciguatera fish poisoning, Canary Islands. Emerg Infect Dis 2005;11:1981−2.

[46] Fraga S, Rodriguez F. Genus *Gambierdiscus* in the Canary Islands (NE Atlantic Ocean) with description of *Gambierdiscus silvae* sp. nov., a new potentially toxic epiphytic benthic dinoflagellate. Protist 2014;165:839−53.

[47] Otero P, Perez S, Alfonso A, Vale C, Rodriguez P, Gouveia NN, et al. First toxin profile of ciguateric fish in Madeira Arquipelago (Europe). Anal Chem 2010;82:6032−9.

[48] Tester PA, Vandersea MW, Buckel CA, Kibler SR, Holland WC, Davenport ED, et al. *Gambierdiscus* (Dinophyceae) species diversity in the flower garden banks National Marine Sanctuary, Northern Gulf of Mexico, USA. Harmful Algae 2013;29:1−9.

[49] Gingold DB, Strickland MJ, Hess JJ. Ciguatera fish poisoning and climate change: analysis of National Poison Center Data in the United States, 2001−2011. Environ Health Perspect 2014;122:580−6.