Chapter 11

CIGUATERA-CAUSING DINOFLAGELLATES IN THE GENERA *GAMBIERDISCUS* AND *FUKUYOA*: DISTRIBUTION, ECOPHYSIOLOGY AND TOXICOLOGY

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ABSTRACT

Ciguatera poisoning results from the consumption of fish and marine invertebrates contaminated with lipid soluble toxins known as ciguatoxins (CTXs) that are produced by benthic dinoflagellates in the genera *Gambierdiscus* and *Fukuyoa*. Overall, 16 species of *Gambierdiscus* and three closely related *Fukuyoa* species are now recognized worldwide.

Occurrence data clearly highlight the current geographical expansion of these organisms from tropical and sub-tropical waters to temperate-like areas, a likely consequence of climate change. Numerous studies have examined *Gambierdiscus/ Fukuyoa* spp. *in vitro* growth responses under varying environmental factors. Results confirm that differences in both tolerance and optimum growth ranges exist not only across species, but across strains as well.

Gambierdiscus/Fukuyoa spp. are the potential source of at least six families of cyclic polyether compounds whose contribution to ciguatera syndrome (except for CTXs) as well as ecological relevance remain to be ascertained. Factors governing toxinogenesis in these organisms are not well understood, but several studies have provided evidence that this functional trait may depend on a combination of abiotic and biotic (including genetic) factors.

Despite the significant advances achieved in the understanding of this phenomenon, ciguatera incidents remain difficult to predict, and their recent expansion to novel areas continues to pose a serious threat to the public health, lifestyle and economy of world populations. Suggested areas for future research efforts will be discussed.

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1. INTRODUCTION

Ciguatera poisoning represents the most common non-bacterial seafood intoxication globally, and results from the consumption of fish that have accumulated lipid soluble toxins known as ciguatoxins (CTXs) [1 and references therein]. Yet, other marine organisms that are also highly prized by island communities such as bivalves (e.g., giant clams), echinoderms (*e.g*., sea urchins) and gastropods (e.g., trochus) have been found to be potential vectors for human poisonings by CTXs [2-5]. CTXs are produced by benthic dinoflagellates in the genus *Gambierdiscus* and *Fukuyoa* (Figure 1) that grow preferentially within mixed algal 'turfs' covering degraded coral substrates [6], although these organisms may also be found in sand, coral, detritus and other surfaces (Figure 2). CTXs enter the coral reef food web through grazing by herbivores and detritivores and are further accumulated and bio-transformed in carnivores through predation [7].
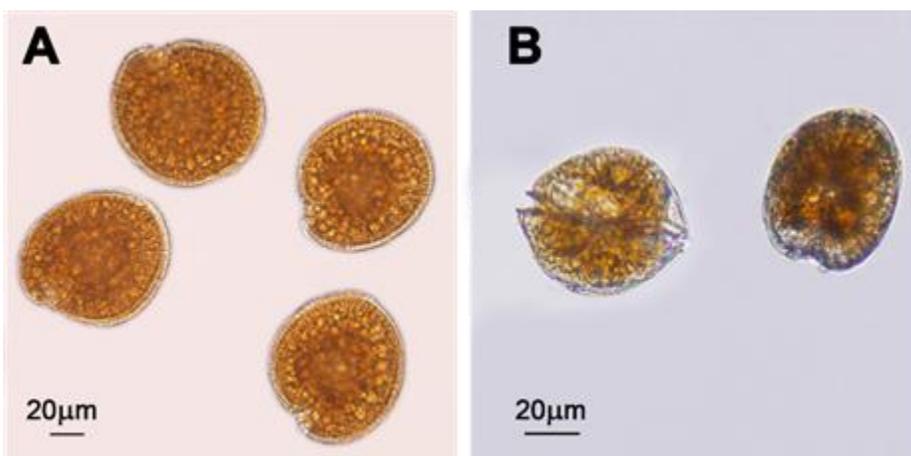

Figure 1. *Gambierdiscus* and *Fukuyoa* cells under light microscopy. (A) *Gambierdiscus toxicus* (© ILM); (B) *Fukuyoa paulensis* (© Lesley Rhodes, Cawthron Institute).

Ciguatera syndrome is characterized by a complex symptomatology, including gastrointestinal, neurological, cardiovascular and general disorders [8, 9, and references therein], that vary between individuals [10] and is often complicated by chronic manifestations lasting months to years [11, 12]. Fortunately, mortality is rare (<0.1%), but the high morbidity of this debilitating and sometimes long-lasting illness makes it a prominent problem for recreational and subsistence fisheries worldwide. Over the past decades, the frequency and distribution of ciguatera have allegedly expanded, a likely consequence of increased human activities and climate change [13-18].

A wealth of data on the main causative agent of ciguatera, *Gambierdiscus* spp., can be found in the literature. However the resurgence of scientific interest and increasing research efforts noticeable worldwide in the past decade have led to recent advances in the understanding of this organism, particularly with respect to the discovery of novel species and

novel compounds. The purpose of this book chapter is to provide an update of the current state of knowledge on the taxonomy, distribution, ecophysiology and toxicology of the ciguatera-causing dinoflagellates *Gambierdiscus* and *Fukuyoa*. A further section will deal with the global socio-economic impacts of ciguatera poisoning, in light of the recent expansion of ciguatera to novel (temperate) areas and the significant burden it represents for world populations. The concluding section will focus on some of the remaining knowledge gaps in this field of research in order to develop reliable control strategies of ciguatera poisoning.

2. BIODIVERSITY OF *GAMBIERDISCUS* AND *FUKUYOA* SPP.

Species composition of *Gambierdiscus* assemblages, and particularly the presence of highly toxic species or strains in a given area, is arguably one of the main driving factors for elevated ciguatera incidence rates and severity of outbreaks [4, 19, 20]. The accurate identification of *Gambierdiscus* species and their associated toxicity is therefore crucial to help predict the potential emergence of ciguatera risk.

Until 1995, *Gambierdiscus* was regarded as a monotypic taxon with all *Gambierdiscus* cells recorded as *G. toxicus* [21]. However, the significant progress achieved over the past two decades in taxonomic studies of this genus, most notably the identification of reliable molecular markers, has allowed for the description of new species of *Gambierdiscus*, suggesting that many of the reports of *G. toxicus* in the early literature may actually concern other species. As a matter of fact, it was further concluded that the original description of *G. toxicus* by Adachi and Fukuyo (1979) [21] likely included multiple species [22], and eventually led to the description of a new epitype of *G. toxicus* in 2009 [23, 24].

Modern taxonomy of *Gambierdiscus* species currently uses both morphological characteristics and phylogenetic analyses. Morphotaxonomy traditionally considers distinguishing characteristics such as cell shape (globular vs. lenticular), cell surface (smooth vs. areolated), cell size, or size and shape of specific thecal plates (e.g., 1p, 2', or 4" using the Kofoid tabulation system) to differentiate between isolates. These key characteristics can be found in detail in the original descriptions of *Gambierdiscus*/*Fukuyoa* species. Molecular analyses rather focus on molecular markers such as nuclear-encoded ribosomal RNA genes (5.8S, SSU and LSU rDNA), since noted plasticity in the morphology of cells can lead to inaccurate identification, particularly when comparing cultured clones to cells collected from the field [25]. Different molecular techniques are currently available, including Polymerase Chain Reaction (PCR), Restriction Fragment Length Polymorphism (RFLP), Fluorescent *In Situ* Hybridization (FISH) probes or complete sequencing of the targeted genes [20, 26].

Overall, 16 species of *Gambierdiscus* are now recognized worldwide: *G. toxicus*, *G. belizeanus*, *G. australes*, *G. pacificus*, *G. polynesiensis*, *G. caribaeus*, *G. carolinianus*, *G. carpenteri*, *G. excentricus*, *G. scabrosus*, *G. silvae*, *G. balechii*, *G. cheloniae*, *G. lapillus*, *G. honu* and *G. jejuensis* [21, 23, 25, 27-35]. In addition, two globular *Gambierdiscus* species have recently been reclassified as *Fukuyoa yasumotoi* and *F. ruetzleri*, with a new species described as *F. paulensis* [23, 36, 37]. Formal classification is also pending for several unnamed genetic clades (i.e., *Gambierdiscus* sp. ribotypes and *Gambierdiscus* sp. types) which could represent new undescribed species, as it was the case for *G. silvae*, *G. scabrosus*,

G. jejuensis and *G. balechii* previously known as *Gambierdiscus* sp. ribotype 1, *Gambierdiscus* sp. type 1, 2 and 6, respectively [29, 30, 35, 38]. It is likely that more species will be characterized in the coming years as more extensive samplings are conducted in areas that are still understudied such as the Indian Ocean or temperate locales.

Of note, the generalization of the molecular approach to ciguatera species identification has also fostered the development of novel detection tools operational straightforward in ciguatera risk assessment programs. Indeed, semi-quantitative PCR assays are now available for the detection and enumeration of the following species/types in environmental samples: *G. belizeanus, G. caribaeus, G. carpenteri, G. carolinianus, G. ruetzleri (renamed Fukuyoa ruetzleri)* and *Gambierdiscus* sp. ribotype 2 [26], *G. scabrosus*, and *Gambierdiscus* sp. type 2 and 3 [39], *G. polynesiensis, G. toxicus, G. pacificus* and *G. australes* [4], *G. lapillus* [40], and *G. excentricus* and *G. silvae* [41]. Recently, Smith et al. (2017) [42] have proposed the use of metabarcoding techniques as a useful approach for the high-throughput screening of ciguatera-related harmful algal blooms (HAB) species.

3. GLOBAL DISTRIBUTION OF *GAMBIERDISCUS* AND *FUKUYOA* SPP.

Numerous reports of the presence of *Gambierdiscus* in samples collected from the eastern Atlantic region, the Caribbean and Western Atlantic region, Central and Western Pacific, Southeast Asia and Indian Ocean can be found in the literature [24 and references therein]. For several of these locales, the species diversity still remains unknown. As mentioned above, earlier reports of *G. toxicus* as a single cosmopolitan species with a seemingly worldwide circumtropical distribution needs to be reconsidered [23, 24 and references therein, 43, 44].

Gambierdiscus spp. are preferentially found in tropical and sub-tropical waters of the globe between 35°N and 35°S [45], but recent studies show that *Gambierdiscus* and/or *Fukuyoa* spp. are presently established in temperate-like areas as well, including Korea [35, 46] Japan [39], the Kermadec Islands (New-Zealand) [47, 48], Southern Australia [49], the Northern Gulf of Mexico [50], and the Mediterranean Sea [51, 52] (Table 1). There is concern that the geographic range of these two genera, and subsequently of ciguatera outbreaks, will continue to expand as sea surface temperatures rise [53, 54]. Indeed, cyclical weather patterns such as El Niño - which is associated with unusual warming waters in the Pacific - have resulted in spike in ciguatera cases in Kiribati, Western Samoa, Tuvalu and Cook Islands [55]. Similarly, Gingold et al. (2014) [56] found an association between ciguatera poisoning (CP) incidence and warmer sea surface temperatures (SST) in the Caribbean basin. Based on water temperature projections over the coming century, a substantial shift in both the distribution and abundance of ciguatera dinoflagellates is to be expected [57, 58], with some species becoming dominant whereas others will become less prevalent. In the long-term, however, temperatures may get too warm according to Llewellyn (2010) [59], thereby hindering *Gambierdiscus/Fukyoa* growth and resulting in a lower risk of ciguatera.

Table 1. Global distribution of *Gambierdiscus* and *Fukuyoa* species and phylotypes. For some of the locations, (*) indicate species which were identified using solely morphological characteristics. Positive confirmation of their identity will require further phylogenetic analyses

Locations	Species or phylotypes	References
Pacific Ocean		
Australia	*G. belizeanus, G. carpenteri, G. honu, G. lapillus, G. toxicus, F. paulensis*	[33, 47, 48, 49, 164, 198, 238, 239]
Cook Islands	*G. australes, G. pacificus, G. polynesiensis, G. cheloniae, G. honu, G. lapillus*	[4, 25, 32, 34, 44, 47, 117, 165, 240]
Fiji	*G. carpenteri, G. toxicus*	[44, 47]
French Polynesia	*G. australes, G. caribaeus, G. carpenteri, G. pacificus, G. polynesiensis, G. toxicus*	[4, 21, 25, 44, 86, 241]
New Zealand	*Mainland: F. paulensis*	[42]
	Kermadec Islands: G. australes, G. honu, G. polynesiensis	[48, 132, 133]
Guam	*G. carpenteri, G. toxicus*	[23, 47, 241]
Hawaii	*G. australes, G. caribaeus, G. carpenteri, G. toxicus*	[23, 44, 47, 86, 241]
Kiribati	*G. balechii, G. belizeanus, G. carpenteri, G. pacificus, Gambierdiscus sp. type 4, 5*	[38, 242]
Marshall Islands	*G. pacificus, G. toxicus*	[44, 47]
New Caledonia	*G. toxicus*	[25]
Palau	*G. caribaeus, G. toxicus*	[23, 44, 47]
Tonga	*G. australes, G. honu, G. pacificus*	[47]
Caribbean Sea		
Aruba	*G. carolinianus, G. carpenteri*	[19, 24037]
Belize	*G. belizeanus, G. caribaeus, G. carolinianus, G. carpenteri, G. silvae, F. rueztleri, Gambierdiscus ribotype 2*	[23, 27, 44, 86, 240, 241]
Cayman Islands	*G. caribaeus*	[23, 44, 86, 241]
Curaçao	*G. silvae*	[240]
Jamaica	*G. caribaeus, G. carolinianus, G. carpenteri,*	[23, 44, 86, 241]
Martinique	*Gambierdiscus ribotype 2*	[44, 86, 241]
Mexico	*G. belizeanus, G. caribaeus, G. carolinianus, G. carpenteri, G. toxicus, F. yasumotoi*	[41, 86, 240, 241, 243]
Puerto Rico	*Gambierdiscus ribotype 2*	[44, 86, 241]
St Barthélemy	*G. belizeanus*	[20, 23, 86, 241]
St Maarten	*G. belizeanus, G. carolinianus, Gambierdiscus ribotype 2*	[86, 240]
Turks & Caicos	*G. belizeanus*	[240]
US Virgin Islands	*G. belizeanus, G. caribaeus, G. carolinianus, G. carpenteri, G. silvae, Gambierdiscus ribotype 2*	[20, 86, 240, 241]
Gulf of Mexico		
Dry Tortugas	*G. caribaeus, G. carpenteri*	[86, 241]
Florida Keys	*G. belizeanus, G. caribaeus, G. carolinianus, G. carpenteri, G. excentricus, G. silvae, F. yasumotoi, Gambierdiscus ribotype 2*	[20, 23, 44, 107, 240, 241]
Flower Garden Banks	*G. belizeanus, G. caribaeus, G. carolinianus, G. carpenteri, F. rueztleri, Gambierdiscus ribotype 2*	[19, 86, 240, 241]
Indian Ocean		
La Réunion	*G. belizeanus*, G. toxicus**	[25, 244]
Mauritius	*G. toxicus**	[245]
Tanzania	*G. toxicus**	[246]

Table 1. (Continued)

Locations	Species or phylotypes	References
Atlantic Ocean		
Bahamas	*G. caribaeus, G. carolinianus*	[20, 44]
Bermuda	*G. carolinianus*	[44]
Brazil	*G. excentricus, G. silvae, F. paulensis*	[37, 86, 247, 248]
Canary Islands	*G. australes, G. caribaeus, G. carolinianus, G. excentricus, G. silvae, Gambierdiscus ribotype 3*	[28, 30, 86, 166, 249]
Florida	*G. belizeanus, G. caribaeus, G. carolinianus, G. carpenteri, G. excentricus, F. rueztleri*	[19, 240, 241]
Madeira	*G. australes*	[166, 241]
Morocco	*G. excentricus*	[30]
North Carolina	*G. carolinianus, F. rueztleri*	[19, 23, 241]
Mediterranean Sea		
Balearic Islands	*G. australes, F. paulensis*	[52, 127]
Crete	*G. carolinianus*	[86, 241]
Red Sea		
Jordan	*G.* cf. *belizeanus, F. yasumotoi*	[250]
Saudi Arabia	*G. belizeanus*	[251]
Persian Gulf		
Kuwait	*F. yasumotoi*	[250]
Arabian Gulf		
Pakistan	*G. australes, G. belizeanus, G. polynesiensis, G. toxicus, F. yasumotoi*	[252]
Asia		
Borneo	*G. belizeanus*, G. pacificus**	[253, 254]
China	*G. australes, G. caribaeus, G. pacificus, F. rueztleri*	[240, 255]
Indonesia	*G. balechii*	[31]
Japan	*G. australes, G. scabrosus, F. yasumotoi, Gambierdiscus sp. type 2, 3*	[20, 29, 85, 86, 101, 167]
Korea	*G. caribaeus, G. jejuensis, F. yasumotoi*	[35, 46, 256]
Malaysia	*G. balechii, G. caribaeus, G. carpenteri, G. honu, G. pacificus, F. yasumotoi*	[38, 47, 86, 193, 240]
Phillipines	*G. carpenteri*	[70]
Singapore	*F. yasumotoi*	[36]
Thailand	*G. caribaeus*	[257]
Vietnam	*G. pacificus*, G. toxicus*, G. polynesiensis*, F. yasumotoi**	[128, 258]
China	*G. australes, G. caribaeus, G. pacificus, F. rueztleri*	[240, 255]

Table 1 provides an updated summary of the current distribution of all known *Gambierdiscus* and *Fukuyoa* species. These global occurrence data were collated from studies which used either morphological and/or molecular techniques to identify species. Interestingly, in some of these locations, the presence of ciguatera-related dinoflagellates is consistent with the report of ciguatera cases decades earlier [60-63]. In addition, *Gambierdiscu*s and/or *Fukuyoa* have also been reported from other regions of the world, such as Tonga [42], several locations in Latin America such as Mexico, Cuba, Guatemala, El Salvador, Costa Rica, Colombia, etc. [64 and references therein, 65, 66], Morocco and Crete [51], Hong Kong waters [67], and the Lesser Antilles [68], nevertheless, the exact species are yet to be determined.

Occurence data suggest that some of these species seem to be limited to specific areas of the globe (i.e., *G. excentricus* and *G. scabrosus)*, whereas others are characterized by a more cosmopolitan distribution (i.e., *G. belizeanus, G. caribaeus, G. carpenteri* and *F. yasumotoi*) (Table 1), consistent with the wider range of tolerance to environmental conditions exhibited by these species *in vitro* [69, 70] (see section 4). Nevertheless, it is likely that, with additional samplings, species now designated as specific to a region will eventually be reported from other locales.

Assessing *Gambierdicus/Fukuyoa* spp. abundance in the environment proves very challenging due to the high variations observed both at a temporal and spatial scale. Too, the notorious patchy distribution of these dinoflagellate even over small distances, and the differences in the algal hosts morphology which can greatly influence abundance estimates are other major impediments to an accurate assessment of population densities [71]. Despite these limitations, the literature survey conducted by Litaker et al. (2010) [44] on *Gambierdiscus* abundance data for the Atlantic and Pacific Oceans showed that 85% of the average values were < 1,000 cells.g^{-1} wet weight (ww) algae, while 10% of the abundance estimates fell between 1,000 and 10,000 cells.g^{-1} ww algae. Such findings have led the authors to speculate that densities > 1,000 cells.g^{-1} ww algae likely correspond to localized blooms conditions that have the higher potential of causing ciguatera events. On the other hand, some studies have stressed the importance to also consider algal host-dinoflagellate associations, which may act as toxin source or sinks, depending on macroalgal palatability [72]. In other words, algae that are actively consumed by herbivores could be responsible for a high toxin flux even at low dinoflagellate densities, whereas unpalatable algae with higher dinoflagellate densities might contribute little to toxin transfer in marine food webs.

4. ECOPHYSIOLOGY

Gambierdiscus/Fukuyoa spp. are regarded as benthic epiphytic organisms, but can occasionally exhibit free-swimming behavior [73-76], suggesting that they may behave as mixotrophs [77]. Although members of this genus survive as photoautotrophs, this hypothesis is consistent with recent findings that complex pathways of N and C utilization are indeed present in this taxon [77]. According to these authors, cells of *G. caribaeus* were able to sustain significant growth in the absence of light when cultured in medium supplemented with an exogenous carbon source. Nonetheless, such findings still await further confirmation since these authors used non-axenic cultures, and previous research showed that this dinoflagellate may require the presence of specific bacteria to maintain growth [78].

The life cycle of *Gambierdiscus* is still poorly documented. Early studies by Hokama et al. (1996) [79] described the succession of six distinct stages in culture: i) a motile free-swimming cell phase at the beginning of the culture, ii) a pre-cyst phase after 2 to 3 weeks, iii) a cyst phase followed by iv) a secondary cyst phase, v) a mitotic phase in which cysts divide, and vi) a terminal phase that may last up to 4-6 months preceding a new cycle. Next, Van Dolah et al. (1995) [80] demonstrated that cell division in *Gambierdiscus* was phased to the diurnal cycle, with cells dividing only during a 3h-window late in the dark phase, when grown in a 16:8 hour light:dark cycle. These authors also documented the role played by a CDC2-like kinase which, like in higher eukaryotes, was expressed constitutively in

Gambierdiscus throughout the cell cycle but activated only during mitotis. Results of a recent study conducted on a *G. balechii* strain allowed to confirm previous findings on a circadian regulation of cell division [81] and that the life cycle of *Gambierdiscus* likely involves both asexual and sexual processes, as speculated by Taylor (1979) [82]. All these observations (cyst-like structures and sexual reproduction) may help explain the exceptional ability of these species to adapt, survive, and even thrive in harsh environmental conditions (see following sections 4.1 and 4.2).

Compared to most planktonic dinoflagellates, *Gambierdiscus*/*Fukuyoa* spp. are considered slow-growing organisms, with growth rate never exceeding 0.5 div.d^{-1} [19, 35, 58, 69, 83-86]. The highest growth rate ever reported for *Gambierdiscus* isolates is 0.55 div.d^{-1} and concerns a Hawaiian strain [87]. Whether there is a relationship between growth rate and cell potency remains unclear, although highly toxic clones in the genus *G. polynesiensis* were found to exhibit relatively low reproductive rates ($\simeq$ 0.13 div.d^{-1}) as compared to non-ciguatoxic strains [83].

4.1. *Gambierdiscus/Fukuyoa* spp. Preferred Habitats

High densities of *Gambierdiscus*/*Fukuyoa* spp. are often observed in disturbed/degraded coral reef habitats [15-17, 44]. Indeed, Lewis (1986) [15] reported that *Gambierdiscus* grows prodigiously following both natural and man-made disturbances of coral reefs. Similarly, while studying the fluctuations of *G. toxicus* populations in a ciguateric site of French Polynesia, Chinain et al. (1999) [17] found that there was an increase in both the density and frequency of *Gambierdiscus* blooms following a severe coral bleaching episode affecting large areas of the study site. A general consensus is that the massive colonization of dead corals by macroalgae provides more substrate for the settlement of epiphytic *Gambierdiscus*/*Fukuyoa* spp. populations, as first hypothesized by Randall (1958) [88]. This may explain why reef disturbances due to extreme climatic events (*e.g.*, hurricanes, heavy rains, coral bleaching) or human activities (*e.g.*, dredging and filling, constructions, military activities) frequently precede ciguatoxic events [1, 13, 14, 89].

It is not clear whether *Gambierdiscus* abundances are subject to seasonality or not, as field studies sometimes showed contradictory conclusions. Chinain et al. (1999) [17] reported that *Gambierdiscus* cell densities were the highest at the beginning and end of the hot season in French Polynesia, consistent with observations from a field survey conducted in Hawaii [57]. Conversely, other studies did not observe seasonal patterns or concluded that highest densities were rather reported in the fall season [79, 90, 91]. In any case, it is likely that seasonal patterns, if any, will be primarily determined by the different temperature tolerances characterizing the various *Gambierdiscus*/*Fukuyoa* species (see the following section 4.2).

Gambierdiscus populations are generally more abundant in habitats where temperatures are comprised between 25 and 30°C [17, 54]. However, early observations from the Florida Keys, U.S. Virgin Islands, Hawaii, and Queensland, that *Gambierdiscus* abundance peak at cooler temperatures seem to contradict this generalization [24 and references therein].

Like other dinoflagellates, *Gambierdiscus spp.* are sensitive to excessive agitation and show a clear preference for calm and stable environments [44, 45, 92]. There are several field observations, however, that tend to contradict this general idea: for instance, in areas such as Mayotte Island, Hawaii or Canary Islands, higher densities of *Gambierdiscus* were actually

found in turbulent winward locations [28, 93, 94]. Small-scale turbulence has been shown to directly influence the physiology of some dinoflagellates by causing cell disruption, alteration of cell division and cell cycle phase duration, and even by affecting toxin production [95, 96]. Nakahara et al. (1996) [75] have observed that turbulence may cause *Gambierdiscus* cells to quickly attach to the surface of the macrophyte. Cells are also often found attached to their algal host by a mucus thread, so as to limit cells dispersal.

Gambierdiscus appears to prefer environments with high, stable salinities, between 28-35 [24 and references therein, 44] but has been reported from areas with extreme lower or upper salinity values such as river outlets [65] or mangrove environments where salinity can exceed 40 [97]. There is evidence, however, that salinity preferences may significantly differ among species [24, 69] (see following section 4.2.).

Many studies have documented the apparent preference of *Gambierdiscus* for specific macroalgal hosts [24 and references therein, 68], but the exact nature of this preference remains elusive. There is some evidence that various macroalgae may supply important growth factors [75, 93, 98-100], but other factors such as algal structure and surface area, or algal class may also play a critical role [6, 72, 76, 98]. According to Bienfang et al. (2008) [45], the occurrence of *these epiphytic organisms* on many macroalgae species suggests opportunism in regard to macroalgal substrate, rather than a regulation of their abundance by specific macroalgal metabolites. Results of a study which examined the epiphytic relationship between *Gambierdiscu*s and 24 different macroalgal species seem to contradict this statement since it was shown that i) cells attached to specific algal species while avoiding others, and ii) certain algal host inhibited cells proliferation while others allowed for their growth [76]. In addition, in the environment, cell densities of epiphytic pennate diatoms on macroalgae have been shown to affect *Gambierdiscus* spp. abundance and therefore, may represent another growth determinant in the same way as sea water temperature, salinity and nutrients [101]. In any case, multiple benefits may result from the association of *Gambierdiscus* spp. with macrophytes: e.g., fixation on a substrate, protection from turbulence, shading from direct sunlight, and access to organic compounds within the thallisphere [102].

Gambierdiscus spp. are able to grow in shaded as well as high-lighted water habitats [50]. In shallow tropical waters, for instance, *Gambierdiscus* populations are often found attached to benthic macrophytes or to drifting algae or detritus [103] where surface irradiances can sometimes exceed 2,000 µmol photons.m^{-2}.s^{-1} [102]. In cultures, however, these organisms seem to be best adapted to relatively low light conditions (50-230 µmol photons.m^{-2}.s^{-1}) and can even sustain growth at irradiances as low as 10 µmol photons.m^{-2}.s^{-1}, which would allow cells to survive at depths > 80-100m in tropical environments [84, 104]. There are actually limited data studies on the vertical distribution of *Gambierdiscus*/*Fukuyoa* spp. [50, 105, 106] but early observations are consistent with *in vitro* observations since the presence of *Gambierdiscus* cells was reported at depths between 30-50m [23, 50, 93, 97]. Furthermore, recent findings clearly suggest the existence of species-specific responses to changing light regimes, with species capable of maintaining growth even when exposed to very high irradiances (> 500 µmol photons.m^{-2}.s^{-1}) [69, 107]. Several behavioral strategies have been suggested to help this organism cope with high irradiances, including cell aggregation, mucus production, use of the three-dimensional structure of the algal host to minimize light exposure and prevent photodamage, as well as physiological responses such as the plasticity of cell size and chlorophyll content [102, 107, 108].
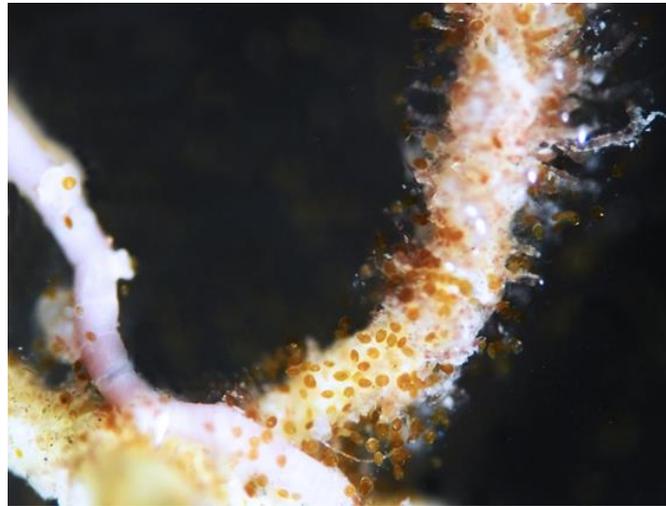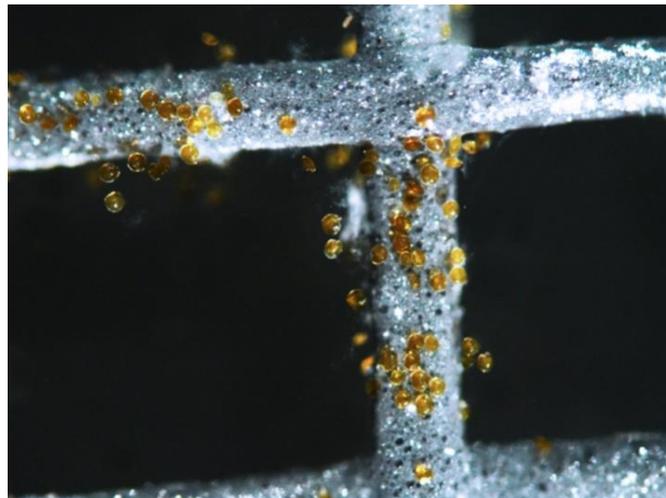
Figure 2. Cells of *Gambierdiscus* sp. attached to natural and artificial substrates. (A) on the thallus of *Jania* sp. (Rhodophyte); (B) on the grilling of a window-screen device (© ILM).

4.2. *In Vitro* Growth

Data regarding *Gambierdiscus/Fukuyoa* spp. growth responses under varying environmental factors are useful to inform predictive models of their abundance, seasonality and global distribution. Early laboratory studies have primarily investigated *Gambierdiscus* sp. optima and limits for temperature, salinity and light factors. Overall, these studies generally agree with field surveys although conflicting results were sometimes reported [see 24 for a review and references therein].

The influence of ambient nutrient concentrations on *Gambierdiscus* populations remains ambiguous, since this topic had been the subject of a limited number of field studies, with

sometimes contradictory conclusions [94, 105, 109]. Similarly, only two laboratory studies have sought to determine the effect of nutrients on *Gambierdiscus* growth: in the first study by Sperr and Doucette (1996) [110], the authors found that growth rates within five isolates remained constant under different N:P ratios, indicating an ability of all clones to maintain high reproductive rates under different nutritional regimes. The second study by Lartigue et al. (2009) [111] examined the effects of different nitrogen sources on the growth of two clones and concluded that nutrient physiologies likely differed between strains. Interestingly, these clones were subsequently classified as two distinct species, namely *G. caribaeus* and *Gambierdiscus* sp. ribotype 2.

As mentioned previously, most of these studies were conducted at a time when *Gambierdiscus* taxonomy was unresolved, so the extent to which growth responses may vary across the multiple species now known in *Gambierdiscus* and *Fukuyoa* genera remains to be clarified. Recent studies have started to provide growth data for the following species/phylotypes: *G. polynesiensis*, *G. australes*, *G. pacificus*, *G. belizeanus*, *G. caribaeus*, *G. carolinianus*, *G. carpenteri*, *G. silvae*, *G. scabrosus*, *F. ruetzleri*, and *Gambierdiscus* spp. types 2, 3, 4 and 5 [69, 70, 83-85, 104, 112]. Results confirm that differences in both tolerance and optimum growth ranges exist not only across species, but across strains as well [70].

5. TOXICOLOGY

5.1. Chemodiversity of Secondary Metabolites

Increasing attention is paid to secondary metabolites produced by microalgae, particularly dinoflagellates due to their potential uses in the biology, biomedical and toxicological fields [113]. These compounds are also ecologically relevant since they are suspected to act as allelochemicals influencing biotic interactions (see section 5.4), and may therefore be involved in structuring microbial communities [114]. The recent development of metabolomics is furthermore a unique opportunity to investigate the chemodiversity of such dinoflagellates, in order to e.g., describe new compounds (including toxins), assess the variations of their productions in response to different stressors, or identify chemical markers at different taxonomic levels (chemotaxonomy) [115].

Gambierdiscus/Fukuyoa species produce several non-structurally related groups of secondary metabolites with a ladder-shaped cyclic polyether backbone: ciguatoxins (CTXs), maitotoxins (MTXs), gambieric acids (GAs), gambierol, gambieroxide and gambierones (Figures 3 & 4). The Table 2 presents the compounds that have been detected in the different *Gambierdiscus/Fukuyoa* species described to date (except for the newly described *G. jejuensis* and *F. yasumotoi* species for which no information are available), through isolation or liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) analyses. As outlined above, before 1999 and the study by Chinain et al. [25] that has introduced molecular analyses, the identification of *Gambierdiscus* species was made solely on the basis of morphological characteristics, leading to potential misidentifications. Thereby, strain identifications prior to 1999 should probably be reassessed, particularly concerning *G. toxicus*.

**Table 2. List of polyether compounds that have been detected
(through isolation or LC-MS/MS analyses) in *Gambierdiscus/Fukuyoa* genera**

Species[a]	P-CTXs	MTXs	Other compounds	References
F. paulensis	P-CTX3 (= 54-deoxy-P-CTX1B)[b] *No P-CTX3B, P-CTX3C, P-CTX4A, P-CTX4B*	*No MTX1*	Gambieric acid A[b] 44-methylgambierone[c]	[49, 127, 132, 133]
F. ruetzleri	*No P-CTX3C and P-CTX4A/B*[d]	*No MTX1, MTX2, MTX4*	44-methylgambierone[c]	[67, 131]
G. australes	*No P-CTX3B, P-CTX3C, P-CTX4A, P-CTX4B*[d]	MTX1 *No MTX2, MTX4*	44-methylgambierone[c]	[32, 47, 48, 117, 121, 131-133, 138, 170]
G. balechii	*No information available*	*No MTX1, MTX2, MTX4*	44-methylgambierone[c]	[131]
G. belizeanus	*No P-CTX3B, P-CTX3C, PCTX4A,P-CTX4B*	*No MTX1, MTX2, MTX4*	Gambierone 44-methylgambierone[c]	[131, 139, 144, 170]
G. caribaeus	*No P-CTX3C and P-CTX4A/B*[d]	MTX2[e] *No MTX1, MTX4*	44-methylgambierone[c]	[131]
G. carolinianus	*No information available*	*No MTX1, MTX2, MTX4*	44-methylgambierone[c]	[131]
G. carpenteri	*No P-CTX3B, P-CTX3C, P-CTX4A, P-CTX4B*[d]	*No MTX1, MTX2, MTX4*	44-methylgambierone[c,f]	[121, 131, 132, 145]
G. cheloniae	*No P-CTX3B, P-CTX3C, P-CTX4A, P-CTX4B*	*No MTX1*	44-methylgambierone[c]	[32, 121, 132]
G. excentricus		MTX2[e] MTX4[h] *No MTX1*	44-methylgambierone[c]	[131]
G. honu	*No P-CTX3B, P-CTX3C, P-CTX4A, P-CTX4B*	*No MTX1*	44-methylgambierone[c]	[34, 121, 132, 133]
G. lapillus	*No P-CTX3B, P-CTX3C, P-CTX4A, P-CTX4B*	*No MTX1*	44-methylgambierone[c]	[33, 121, 145]
G. pacificus		MTX2[e] *No MTX1, MTX4*	44-methylgambierone[c]	[32, 117, 121, 131, 132]
G. polynesiensis	P-CTX3B P-CTX3C M-*seco*-P-CTX3C 2-hydroxy-P-CTX3C P-CTX4A P-CTX4B	*No MTX1*	44-methylgambierone[c]	[32, 83, 117-121]
G. scabrosus	*No information available*	*No MTX1, MTX2, MTX4*	44-methylgambierone[c]	[131]
G. silvae	*No information available*	*No MTX1, MTX2, MTX4*	44-methylgambierone[c]	[131]

Species[a]	P-CTXs	MTXs	Other compounds	References
G. toxicus[j]	P-CTX4A P-CTX4B M-*seco*-P-CTX4A/B P-CTX3B P-CTX3C P-CTX2 (= 52-*epi*-54-deoxy-P-CTX1B) P-CTX3 (= 54-deoxy-P-CTX1B) M-*seco*-P-CTX3C 51-hydroxy-P-CTX3C M-*seco*-P-CTX3C methyl acetal[d]	MTX1 MTX2[e] *No MTX4*	Gambieric acids A-D Gambierol Gambieroxide 44-methylgambierone[c]	[122-126, 131, 134-137, 141-143]
Gambierdiscus sp. ribotype 2	*No information available*	*No MTX1, MTX2, MTX4*	44-methylgambierone[c]	[131]

[a]No information available for *F. yasumotoi* and *G. jejuensis*. [b]Trace amounts. [c]Compound previously identified as MTX3 and renamed 44-methylgambierone by Murray et al. (2019) [138] and Boente-Juncal et al. (2019) [139] who characterized its structure by NMR and MS experiments. [d]2,3-dihydroxy-P-CTX3C tentatively identified by Roeder et al. (2010) [128] on the basis of low resolution LC-MS/MS analyses without reference materials. Furthermore, Pisapia et al. (2017) [131] lately presume that authors may have misidentified 2,3-dihydroxy-P-CTX3C, as it is likely that the actual compound present was the ubiquitous 44-methylgambierone (former MTX3). [e]Tentative identification by Pisapia et al. (2017) [131] on the basis of low resolution LC-MS/MS analyses without reference material. [f]Five temperate *G. carpenteri* strains were found free of 44-methylgambierone (former MTX3) [145], the only ones among 89 *Gambierdiscus* strains tested by Murray et al. (2018) [121]. [g] M/L-seco-P-CTX4A/B, M/L-seco-P-CTX3C/B and tetraseco-P-CTX3C/B tentatively identified by Paz et al. (2011) [130] on the basis of low resolution LC-MS/MS analyses without reference materials. [h]MTX4 is a new compound proposed by Pisapia et al. (2017) [131] on the basis of high resolution LC-MS/MS analyses. [i]P-CTX3C/B, 51-hydroxy-P-CTX3C, M-seco-P-CTX3C, P-CTX4A/B, M-seco-P-CTX4A and C/I-CTX1/2 tentatively identified by Caillaud et al. (2011) [129] on the basis of low resolution LC-MS/MS analyses without reference materials. [j]Potential misidentifications of the species, most likely G. polynesiensis for some Polynesian strains.

Many congeners of CTXs, comprising 13 or 14 rings transfused by ether bonds, have been isolated from dinoflagellates and/or fish [for a review see 116]. They are grouped into three sub-families according to their geographical origin, i.e., Pacific, Caribbean, and Indian CTXs (P-CTXs, C-CTXs and I-CTXs, respectively). Several P-CTXs have been detected in *Gambierdiscus*/*Fukuyoa* species, unlike C-CTXs or I-CTXs which have been found only in fish samples. To date, 11 P-CTXs (Figure 3) were definitely detected in *G. polynesiensis* strains (TB92 and RG92 from French Polynesia, CAWD212 from Cook Islands) [32, 83, 117-121], and/or in some *G. toxicus* strains (GII-1 and RGI-1 from French Polynesia, potential misidentifications of the species, most likely *G. polynesiensis* currently known to be the major toxic species in the South Pacific [116]) [122-126]: P-CTX4A, P-CTX4B, M-*seco*-P-CTX4A/B, P-CTX2 (52-*epi*-54-deoxy-P-CTX1B), P-CTX3 (54-deoxy-P-CTX1B), P-CTX3B, P-CTX3C, 51-hydroxy-P-CTX3C, 2-hydroxy-P-CTX3C, M-*seco*-P-CTX3C, M-*seco*-P-CTX3C methyl acetal. Moreover, trace amounts of P-CTX3 (54-deoxy-CTX1B) was detected in one strain of *F. paulensis* (Dn135EHU from Mediterranean Sea) [127]. In other species of *Gambierdiscus*/*Fukuyoa*, P-CTXs were only tentatively identified on the basis of low resolution LC-MS/MS analyses without reference materials [128-130].

MTX1 (Figure 4a) is the largest non-polymeric molecule described to date in nature, with 32 ether rings and two sodiated sulfate ester groups, having a molecular weight around 3400 Da. It was detected in some *G. australes* [32, 47, 48, 117, 121, 131-133] and *G. toxicus* strains [134-136]. Two other analogues have been reported in the literature but their structures haven't been elucidated yet: MTX2, tentatively detected in some strains of *G. caribaeus*, *G. excentricus*, *G. pacificus* and *G. toxicus* [131, 136], and MTX4, recently detected exclusively

in *G. excentricus* strains [131]. Another putative analogue was initially identified as MTX3 [137] but had a molecular weight much lower than other MTXs and was recently renamed 44-methylgambierone when its structure was finally fully characterized by RMN analyses (see below) [138, 139]. It should be noted that a recent study conducted by Lewis et al. (2016) [140] indicated that several strains of *Gambierdiscus/Fukuyoa* produce multiple MTX congeners, actually more than four for one particular strain of *G. belizeanus,* suggesting a likely broader chemical diversity than what is known so far within MTX group.
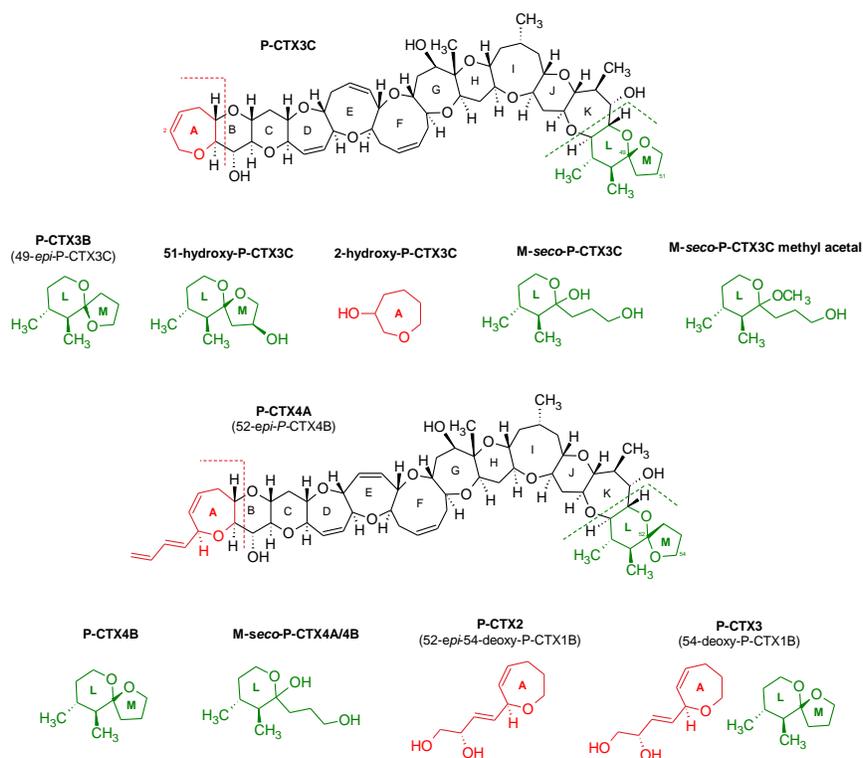

Figure 3. Structures of the P-CTXs definitely detected in *Gambierdiscus/Fukuyoa* genera.
Full structures are represented for P-CTX3C and P-CTX4A whereas only A ring (in red), and/or L/M rings (in green) are represented for other congeners since the rest of their structures is similar to P-CTX3C or P-CTX4A.

Gambieric acids (GA)-A, -B, -C and -D (Figure 4b) were isolated from a strain identified as *G. toxicus* (GII-1 from French Polynesia, potential misidentification of the species) [141] and are composed of nine contiguous ether rings and one isolated tetrahydrofuran. GA-A was also detected in trace amounts in *F. paulensis* (Dn135EHU from Mediterranean Sea) [127].

Gambierol (Figure 4c) was isolated from a strain identified as *G. toxicus* (RGI-1 from French Polynesia, potential misidentification of the species) [142]. It contains a transfused octacyclic polyether core and a skipped triene.

Gambieroxide (Figure 4d) was more recently isolated from a strain identified as *G. toxicus* (GTP2 from French Polynesia) [143]. This polyether compound comprises 12 transfused ether rings and two side chains at the extremities. Its structure is very similar to that of yessotoxin.
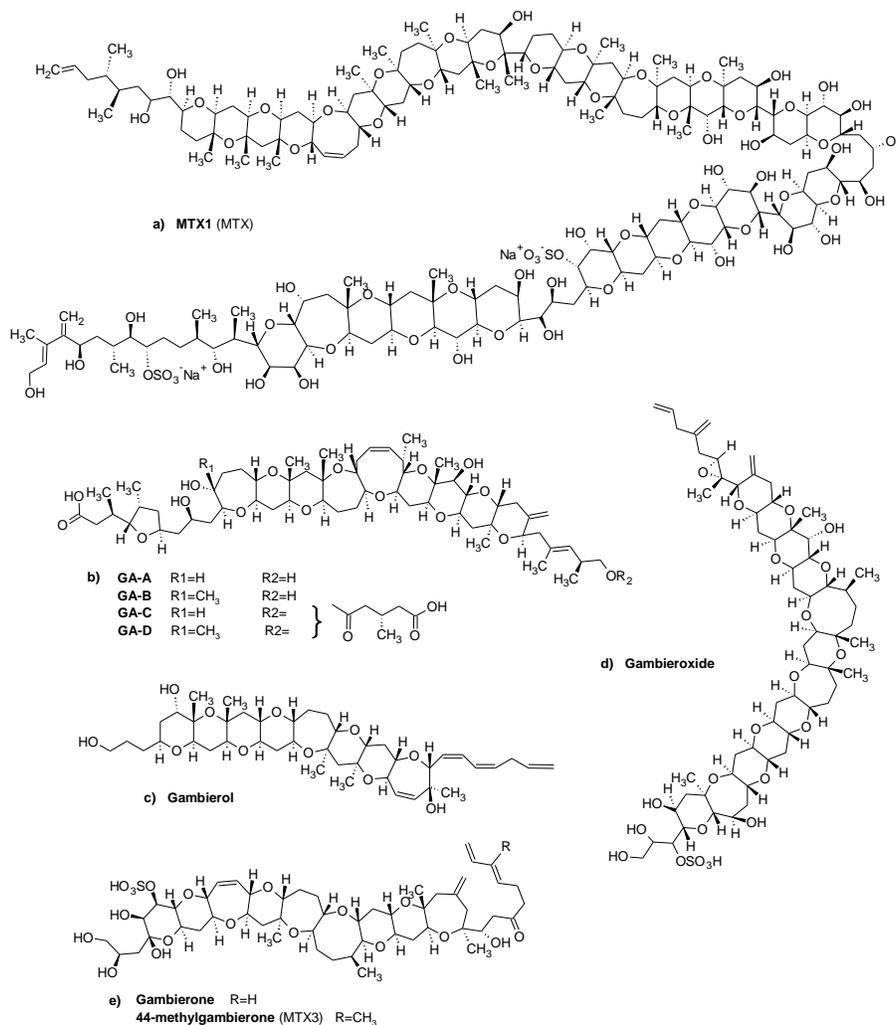
Figure 4. Structures of other polyether compounds isolated from *Gambierdiscus/Fukuyoa* genera.

Finally, gambierone (Figure 4e) was recently isolated from a *G. belizeanus* strain (CCMP401 from Caribbean Sea) [144], as well as its analogue, the 44-methylgambierone (Figure 4e) [138, 139]. The structure of this last molecule was elucidated by another team at the same time after isolation from four *G. australes* strains (Kermadec Islands) [138, 139]. Gambierones are composed of nine transfused rings, a sulfate ester group and a conjugated vinyl end. Before its structure was definitely elucidated, the 44-methylgambierone was reported as MTX3 in numerous studies and has been detected in all *Gambierdiscus/Fukuyoa* species analyzed to date, except for *G. jejuensis* and *F. yasumotoi* for which data are currently unavailable [32-34, 47-49, 67, 117, 121, 131, 132, 145]. An exception concerns temperate clones of *G. carpenteri* which have been found free of 44-methylgambierone [121, 145].

Further characterization of toxin profiles of all known species of *Gambierdiscus/Fukuyoa* is crucial since this information is useful to inform ciguatera risk models. Some authors even speculated that the toxin profiles in the causative dinoflagellates may contribute to shape the

toxin profiles in fish [146] – which have been shown to vary across regions and fish species [123, 147].

5.2. Modes of Action of Bioactive Compounds

CTXs are by far the most studied group due to their direct involvement in ciguatera poisoning. Their major mechanism of toxicity expresses through the binding to site 5 of the α-subunit of the voltage-gate sodium channels (VGSCs) on the neuronal membrane, leading to the persistent activation (opening) of VGSCs which results in cell depolarization at rest and disruption of peripheral and central nerve transmission (e.g., increase in Na^+ influx, enhancement of neuronal excitability, spontaneous and repetitive actions potentials) [for reviews see 148, 149]. The activation of VGSCs by CTXs has been shown to also indirectly disturb the Ca^{2+} homeostasis. Furthermore, some studies indicate that CTXs interact with other targets, such as the voltage-gated potassium channels (VGPCs), resulting in their inhibition and accentuation of the neurocellular perturbations [for reviews see 148, 149]. The multiple effects of CTXs are believed to underly the complex symptomatology observed in CP syndrome. On the contrary, the contribution of the other polyether compounds produced by *Gambierdiscus*/*Fukuyoa* genera to the clinical picture of ciguatera is not yet fully elucidated.

MTX1 is among the most potent marine toxins known to date with an LD_{50} in mice of 50 $ng.kg^{-1}$ [134-136]. Its activity results in a massive calcium influx and a rapid cell death, likely due to a combination of different ion channels' modulation (e.g., nonselective cation channels, voltage-gated calcium channels, transient receptor potential channels) and altering many cellular functions, nevertheless, its primary target and mechanism of action are still unknown [for a review see 139]. MTX2 was shown to produce similar symptoms in mice to those elicited by MTX1, although with lower potency [136], whereas MTX4 was reported to exhibit a toxic effect similar to the one of MTX1 in neuroblastoma cells [131], their mechanisms of action has however not been described yet.

GA-A and GA-B are potent antifungal agents, displaying a remarkable activity against filamentous fungi, while being ineffective against yeasts [150]. GA-A is able to displace the binding of tritiated brevetoxin-3 ([^{3}H]-PbTx-3) to the site 5 of VGSCs in excitable membranes, which is also the binding site of CTXs as describe above [151]. As PbTxs, GA-A could thus be a useful pharmacological tool to study the binding of CTXs to VGSCs.

As GA-A, gambierol acts as a functional antagonist of neurotoxin site 5 on VGSCs [151-153]. In addition, gambierol inhibits VGPCs in neurons, and two of its synthetic analogues have shown great potential for the development of therapeutic tools in autoimmune diseases [154]. Finally, gambierol and some synthetic analogues appear as promising molecules for the treatment of Alzheimer's disease (effects on *N*-methyl-d-aspartate, tau, and amyloid β expressions) [155].

Gambierones seem to share similar biological activities with CTXs. Indeed, gambierone causes VGSCs activation in a similar pattern as CTXs (appearance of sodium currents at hyperpolarized potentials), although with much less potency [144]. Likewise, both gambierone and 44-methylgambierone also induce a small rise in the cytosolic calcium concentration in human cortical neurons, as CTXs [139]. However, a decrease in cell viability in undifferentiated neuroblastoma cells is observed at higher concentrations of 44-

methylgambierone, opening new research avenues on the potential therapeutic effects of this newly characterized molecule [139]. Finally, the expression of ionotropic glutamate receptor has been shown to be modified by chronic exposure of human neurons to gambierones, an alteration that could be involved in the neurological manifestations observed in human CP [139].

5.3. Toxin Production in *Gambierdiscus* and *Fukuyoa* spp.

As mentioned previously, until the late 90s, *Gambierdiscus toxicus* was regarded as the sole origin of CTXs, but recent studies clearly show that this species is only slightly to non-toxic: actually, cultures of *G. toxicus* seem to produce considerable quantities of MTXs but only meager amounts, if any, of CTXs [25, 111]. Too, the lack of assay methods that clearly differentiate CTXs from MTXs in *G. toxicus* cultures may have puzzled early attempts to separate these two toxins [87, 136, 156].

Following the description of novel species in *Gambierdiscus* and *Fukuyoa* genera, many studies aimed at documenting CTXs and MTXs production in these two genera, since these two toxin groups are regarded as the primarily causes of CP (see section 5.2). To this aim, various analytical methods were used, e.g., the mouse biological assay (MBA), mode of action-based methods such as the receptor binding assay (RBA) and the cell based assay using neuroblastoma (CBA-N2a), as well as chemical methods such as LC-MS/MS [157-159].

Tables 3 and 4 provide a tentative overview of all the toxicity data reported across species/strains and geographic locations available in the literature. However, several issues clearly limit data interpretation and comparison between studies: i) the general lack of consensus in extraction protocols and analytical methods used, ii) the fact that these results were obtained under different culture conditions and/or harvesting growth phases, iii) the use of different units to express toxin contents, and iv) several of these studies do not provide quantitative values but, instead, simply inform on the presence/absence of specific toxic compounds.

5.3.1. CTXs Production

Table 3 is a summary of the CTX-related toxicity detected in most of the *Gambierdiscus/Fukuyoa* species known to date (data not available for *F. yasumotoi* and the newly described *G. jejuensis* species).

This table highlights the significant variations observed in CTXs production across species, but also between strains from different geographic origins (intra-specific variance): this is the case for instance for a *F. ruetzleri* strain originating from the Caribbean Sea which was found to be 27-fold and 3.8-fold more toxic than strains from the Gulf of Mexico and the Atlantic Ocean, respectively (Table 3) [19]. Similarly, the CTX-related toxicity in strains of *G. balechii* from the Pacific Ocean was at least 6-fold higher than in strains from Asia. In some instances, toxic and non-toxic strains can even be observed within a given species, as evidenced in a *F. paulensis* strain isolated from the Mediterranean Sea which was found MBA⁺, whereas strains originating from the Pacific and Atlantic Oceans showed no toxicity in MBA [37, 117, 127].

Table 3. CTX production in *Gambierdiscus* and *Fukuyoa* species/phylotypes.
The units commonly used for CTX quantification are indicated in the first line of the
table for each detection method, but different units can also be found in the literature:
([a]) mg.Kg[-1], ([b]) cell.MU[-1], ([c]) pg P-CTX1B/ P-CTX1 eqv.cell[-1],
([d]) pg C-CTX1B eqv.cell[-1], ([e]) pg PbTX-3 eqv.cell[-1]

Species[(*)] and sea	Geographical area	MBA (MU.1,000 cell[-1])	LC-MS/MS (pg CTX.cell[-1])	rRBA (pg PCTX3C eqv.cell[-1])	CBA-N2a (pg PCTX3C eqv.cell[-1])	References
F. paulensis						
Pacific Ocean	New-Zealand	MBA[-]	LC-MS/MS[-]			[117]
Atlantic Ocean	Brazil				CBA-N2a[--]	[37]
Mediterranean Sea	Balearic Islands	MBA[+]	LC-MS/MS[+]			[127]
F. ruetzleri						
Caribbean Sea	Belize		LC-MS/MS[+]		(24.5 ± 0.12) x10^{-3}	[19, 128]
Gulf of Mexico	Northwestern				(6.5 ± 1.47) x10^{-3}	[19]
Atlantic Ocean	North Carolina USA				(0.88 ± 0.40) x10^{-3}	[19]
G. australes						
Pacific Ocean	French Polynesia	4x10^{-4}		[0.017-0.03]		[25, 83]
	Cook Islands	12x10^{-5} [0.8 - 6.3][a]			0.04[c]	[117, 165]
	Hawaii		LC-MS/MS[-]		(2.7 ± 0.9)x10^{-3}	[86, 128]
	Kermadec Islands		LC-MS/MS[-]			[47, 48]
Atlantic Ocean	Canary Islands				[0.6 - 1.4]x10^{-3} [280 - 697]x10^{-3c}	[86, 166]
	Portugal				[200 - 515]x10^{-3c}	[166]
Asia	Japan	670x10^{-4}				[167]
G. balechii						
Pacific Ocean	Kiribati Islands				[0.14 - 19.9]x10^{-3}	[38]
Asia	Malaysia				(1.11 ± 0.19) x10^{-3}	[38]
	Indonesia	MBA[+]			(3.4 ± 1.5) x10^{-3}	[31, 86]
G. belizeanus						
Caribbean Sea	St Barthélémy St Maarten Virgin Island Belize Turks &Caicos			0.123	(0.65 ± 0.10) x10^{-3} (0.49 ± 0.26) x10^{-3} (0.43 ± 0.38) x10^{-3} (2.49 ± 1.28) x10^{-3} (0.51 ± 0.16) x10^{-3}	[19, 25]
Gulf of Mexico	Florida Keys				(0.54 ± 0.03) x10^{-3}	[19]
Red Sea	Saoudi Arabia				[1.02 - 6.5] x10^{-5c}	[251]
G. caribaeus						
Pacific Ocean	Hawaii				(1.6 ± 1.0) x10^{-3}	[86]
Caribbean Sea	Belize Cayman Island Mexico				[0.52 - 0.80] x10^{-3} (0.48 ± 0.04) x10^{-3} (1.29 ± 0.4) x10^{-3}	[19]
Gulf of Mexico	Florida Keys				(0.19 ± 0.03) x10^{-3}	[19]
Asia	Thailand	$\geq$ 100x10^{-4}				[112]

Species[*] occurrence	Geographical area	MBA (MU.1,000 cell^{-1})	LC-MS/MS (pg CTX.cell^{-1})	rRBA (pg PCTX3C eqv.cell^{-1})	CBA-N2a (pg PCTX3C eqv.cell^{-1})	References
G. carolinianus						
Caribbean Sea	Aruba Jamaica Puerto Rico St Maarten				(1.03 ± 0.94) x10^{-3} (0.10 ± 0.03) x10^{-3} (0.02 ± 0.01) x10^{-3} (0.18 ± 0.06) x10^{-3}	[19]
Mediterranean Sea	Crete				(3.3 ± 0.6) x10^{-3}	[86]
G. carpenteri						
Pacific Ocean	Hawaii				(1.4 ± 0.6) x10^{-3}	[86]
Caribbean Sea	Aruba Belize Jamaica Mexico				(0.71 ± 0.21) x10^{-3} (0.29 ± 0.16) x10^{-3} (0.93 ± 0.17) x10^{-3} (1.14 ± 0.18) x10^{-3}	[19]
Gulf of Mexico	Flower Garden Banks				(1.37 ± 0.30) x10^{-3}	[19]
Asia	Philipines			[1 – 7.48][e]		[70]
G. cheloniae						
Pacific Ocean	Cook Islands	[0.32 - 1.58][a]	LC-MS/MS[-]			[32, 34]
G. excentricus						
Gulf of Mexico	Florida				0.469 ± 0.01	[19]
Atlantic Ocean	Canary Islands				1.43 ± 0.05 [0.37 - 1.10][c]	[28, 86]
G. honu						
Pacific Ocean	Cook Islands	0.2[a]				[32, 34]
G. lapillus						
Pacific Ocean	Australia	[0.78 - 150][a]	LC-MS/MS[-]			[33]
G. pacificus						
Pacific Ocean	French Polynesia	9x10^{-4}		r-RBA[-]	[5.44x10^{-4} - 13.5x10^{-3}]	[5, 25, 83, 86]
	Cooks Islands	0.8[a]	LC-MS/MS[-]			[117]
	Republic of Kiribati				(0.011)x10^{-3c}	[242]
Asia	Malaysia				[31.7 - 75.8]x10^{-3}	[129]
G. polynesiensis						
Pacific Ocean	French Polynesia	[13x10^{-5}- 1500x10^{-4}]		[2.8 - 4.5]	[1.2 - 20.9]	[4, 5, 25, 83, 118, 119, 160, 162]
	Cook Islands	1.0[a]	18.2			[32, 117]
G. scabrosus						
Asia	Japan	20x10^{-4}			(27.9 ± 3.8) x10^{-3}	[86, 167]
G. silvae						
Caribbean Sea	Curacao				(19.6 ± 4.21)x10^{-3}	[19]
Atlantic Ocean	Canary Islands				[10.3 - 12.4] x10^{-3}	[86]
G. toxicus						
Pacific Ocean	French Polynesia	1 100 $\pm$ 164[b] MBA-				[25, 83, 156]

Table 3. (Continued)

Species[(*)] and sea	Geographical area	MBA (MU.1,000 cell[-1])	LC-MS/MS (pg CTX.cell[-1])	rRBA (pg PCTX3C eqv.cell[-1])	CBA-N2a (pg PCTX3C eqv.cell[-1])	References
	Australia	MBA-		[0.022-0.028]		[136]
Caribbean Sea	Belize Martinique				[1.3-8.7]x10[-3d] [30.7-54.3]x10[-3d]	[111]
Gulf of Mexico	Florida, USA	[250 - 16 392][b]				[91]
Gambierdiscus sp. ribotype 2						
Caribbean Sea	Martinique Puerto Rico Virgin Islands St Maarten Belize				$(10.9 \pm 0.36) \times 10^{-3}$ $(6.63 \pm 0.54) \times 10^{-3}$ $(4.99 \pm 0.38) \times 10^{-3}$ $(4.66 \pm 1.01) \times 10^{-3}$ $(5.9 \pm 0.8) \times 10^{-3}$	[19]

[(*)] No information available for *F. yasumotoi* and *G. jejuensis*.

Based on Table 3, toxic species can be classified into three distinct groups:

I. a first group of species characterized by a CTXs production of the order of femtograms ($< 4.0 \times 10^{-3}$ pg P-CTX3C eqv.cell[-1], as assessed by CBA-N2a). This group comprises *G. belizeanus*, *G. caribaeus, G. carolinianus* and *G. carpenteri*, with the lowest toxicity recorded in a *G. belizeanus* strain collected from the Red Sea (Table 3).

II. a second group of species which display a toxicity within the range of femtograms ($> 4.0 \times 10^{-3}$ pg P-CTX3C eqv.cell[-1]) up to < 1 pg P-CTX3C eqv.cell[-1], which includes *G. australes*, *G. pacificus, G. scabrosus, G. silvae, G. toxicus*, and *Gambierdiscus* ribotype 2. An exception concerns *G. excentricus* whose toxicity ranged from 0.47 up to 1.43 pg P-CTX3C eqv.cell[-1] in the Atlantic Ocean, although the exact nature of the CTX analogues involved remains to be determined (Tables 2 and 3) [19, 28, 86]. Further investigations are also required to characterize the CTX profiles in *G. cheloniae*, *G. honu* and *G. lapillus* whose extracts showed a significant CTX-like activity on mice that could not be linked however to the presence of either P-CTX3B, -3C, -4A or -4B (Table 2) [32-34].

III. a third group composed exclusively of strains of *G. polynesiensis*, a species allegedly endemic to the Pacific Ocean which is recognized as the highest CTXs producer known to date. Published toxicity data for this species range from 1.2 up to to 20.9 pg P-CTX3C eqv.cell[-1], as assessed by either CBA-N2a, r-RBA or LC-MS/MS [4, 5, 25, 83, 117, 118, 160-162].

Although *G. excentricus* strains have been found to be twice to 14-fold less toxic than *G. polynesiensis* strains, these data suggest that the presence of these two species in a given area could be used as a CP high-risk biomarker, since they are the source of a CTXs reservoir that can be rapidly transferred through the trophic chain via the herbivores [160, 163].

5.3.2. MTXs Production

The contribution of MTXs in CP symptomatology is still the matter of current debate: indeed, because of their low intestinal absorption due to their high molecular weight and hydrophilicity, MTXs are believed to poorly contribute to ciguatera poisoning unless gut and liver tissues of fish are consumed [164].

Table 4 summarizes the MTXs production reported in *Gambierdiscus* and *Fukuyoa* species/phylotypes. It should be noted that the putative MTX3 (p-MTX3) reported in all the studies cited in this section, corresponds in fact to 44-methylgambierone which has been recently characterized [138, 139].

Table 4. MTX production in *Gambierdiscus* and *Fukuyoa* species/phylotypes.
The units commonly used for MTX quantification are indicated in the first line of the table for each detection method, but different units can also be found in the literature:
(ª) mg.Kg^{-1}, (ᵇ) pg pMTX-1.cell^{-1}, (ᶜ) pg MTX4.cell^{-1}

Species[*]	Geographical area	MBA (MU.1,000 cell^{-1})	LC-MS/MS (pg MTX.cell^{-1})	CBA-N2a (pg MTX eqv.cell^{-1})	References
F. paulensis					
Mediterranean Sea	Balearic Islands	MBA$^+$			[127]
Fukuyoa ruetzleri					
Caribbean Sea	Belize		LC-MS/MS$^-$		[128, 131]
Gulf of Mexico	Flower Garden Banks		LC-MS/MS$^-$		[131]
Fukuyoa yasumotoi					
Asia	Singapore	MBA$^+$	-		[36]
G. australes					
Pacific Ocean	French Polynesia	0.2 MBA$^-$			[25, 83]
	Cook Islands		[2.0 - 8.9]^b		[117, 132]
	Hawaii		LC-MS/MS$^-$	(5.5 ± 0.5)	[86]
	Kermadec Islands		[0.3-36.6]^b		[47, 48]
Atlantic Ocean	Canary Islands			[4.3 – 4.7] [227-275]	[86, 166]
Asia	Japan	67x10^{-4}			[167]
G. balechii					
Asia	Indonesia	MBA+		(19.9 ± 2.9)	[31, 86]
G. belizeanus					
Caribbean Sea	St Barthélémy Virgin Island		LC-MS/MS$^-$		[131]
Gulf of Mexico	Florida Keys		LC-MS/MS$^-$		[131]
G. caribaeus					
Pacific Ocean	Hawaii		LC-MS/MS$^+$	(5.3 ± 1.0)	[86, 131]
Caribbean Sea	Belize Cayman Island Mexico		LC-MS/MS$^+$		[131]
Gulf of Mexico	Florida		LC-MS/MS$^+$		[131]

Table 4. (Continued)

Species[*]	Geographical area	MBA (MU.1,000 cell^{-1})	LC-MS/MS (pg MTX.cell^{-1})	CBA-N2a (pg MTX eqv.cell^{-1})	References
G. carolinianus					
Caribbean Sea	Puerto Rico		LC-MS/MS$^-$		[131]
Gulf of Mexico	Dry tortugas		LC-MS/MS$^-$		[131]
Mediterranean Sea	Crete		LC-MS/MS$^-$	(10.6 ± 0.4)	[86, 131]
G. carpenteri					
Pacific Ocean	Hawaii		LC-MS/MS$^-$	(6.3 ± 1.9)	[85]
Caribbean Sea	Belize		LC-MS/MS$^-$		[131]
	Jamaica		LC-MS/MS$^-$		[131]
Gulf of Mexico	Flower Garden Banks		LC-MS/MS$^-$		[131]
G. cheloniae					
Pacific Ocean	Cook Islands	[0.32-1.58]^a			[32, 34]
G. excentricus					
Atlantic Ocean	Canary Islands		[13.0 – 72.8]^c	[0.48 – 1.38] (85.7 ± 41.5)	[28, 86, 131]
	Brazil		[16.0 -19.8]^c		[131]
Gulf of Mexico	Florida		22.9^c		[131]
G. honu					
Pacific Ocean	Cook Islands	0.2^a			[34]
	Kermadec Islands	0.2^a			[34]
G. lapillus					
Pacific Ocean	Australia	MBA$^+$			[33]
G. pacificus					
Pacific Ocean	French Polynesia	0.7	LC-MS/MS$^+$	20.1 ± 5.9	[25, 86, 131]
Asia	Malaysia		LC-MS/MS$^+$		[129, 131]
G. polynesiensis					
Pacific Ocean	French Polynesia	[0.06-0.1]			[25]
	Cook Islands	7.9^a	LC-MS/MS$^-$		[117]
G. scabrosus					
Asia	Japan	67x10^{-4}		(1.5 ± 0.2)	[86, 167]
G. silvae					
Atlantic Ocean	Brazil		LC-MS/MS$^-$		[131]
	Canary Islands		LC-MS/MS$^-$	[2.2 – 3.3]	[86, 131]
G. toxicus					
Pacific Ocean	French Polynesia	0.7	LC-MS/MS$^-$		[25, 86]
	New Caledonia	0.6			[25]
Indian Ocean	La Réunion	1.7	LC-MS/MS$^-$		[25]
Gambierdiscus ribotype 2					
Caribbean Sea	Belize		LC-MS/MS$^-$		[131]
	Puerto rico		LC-MS/MS$^-$		[131]
	St Maarten		LC-MS/MS$^-$		[131]

[*] No information available for *F. yasumotoi* and *G. jejuensis*.

Whereas CTXs production is seemingly restricted to a small number of strains/species, MTX compounds appear to be produced by a large number of *Gambierdiscus/Fukuyoa* species, sometimes in copious amounts [86, 131, 132, 165, 166]. Conversely, based on these

data, three species/phylotypes seem to be unable to produce MTX compounds: *F. ruetzleri, G. belizeanus*, and *Gambierdiscus* ribotype 2, as well as *F. yasumotoi*.

So far, the highest MTX-related toxicity to mice was evidenced in a *G. toxicus* strain originating from La Réunion Island. *G. caribaeus, G. carpenteri, G. scabrosus*, and *G. silvae* were found to produce less than 10 pg MTX eqv.cell^{-1} as assessed by CBA-N2a, while MTX production in *G. balechii, G. carolinianus* and *G. pacificus* produce up to 20 pg MTX eqv.cell^{-1}. As for *G. australes* and *G. excentricus*, both species show a wider range of MTXs production, ranging from 4.3 to 275 and 0.48 to 85.7 pg MTX eqv.cell^{-1}, respectively (Table 4).

It has been suggested that the ability to produce CTXs and MTXs is a stable characteristic in *Gambierdiscus* strains, which is maintained even years after their isolation and acclimatation to laboratory conditions [25, 32, 47, 48, 83, 117, 131, 166, 167]. This observation has led to the speculation that toxin production is genetically determined in this dinoflagellate. However, the significant variation observed in toxicity within and among species [e.g., 19, 83, 86, 110, 131, 168, 169] suggests that this functional trait may also depend on a combination of environmental factors, both biotic and abiotic drivers, as in many other phytoplankton taxa.

5.3.3. Biotic Factors Influencing Toxin Production in Gambierdiscus and Fukuyoa Spp.

5.3.3.1. Genetics of Toxin Production

In the Eukaryote kingdom, *Gambierdiscus* species are among the organisms with the largest genomes, e.g., 32.5 and 35 Gbp for *G. australes* and *G. belizeanus*, respectively [170]. However, very little is known on the biogenesis of CTXs and MTXs and even less on the genes responsible for the production of these toxins in *Gambierdiscus/Fukuyoa* genera.

CTXs and MTXs are polyether ladder compounds that have a polyketide origin. Polyketides are synthesized by specific enzymes called polyketide synthases (PKSs) through a series of condensation and reduction steps of acyl monomers. PKS enzymes are multi-functional complexes consisting of a minimal set of catalytic domains, namely ketoacylsynthase (KS), acyl transferase (AT) and acyl carrier protein (ACP), which are required for function. Three further domains ketoacylreductases (KR), dehydrases (DH) and enolreductases (ER) can be optionally present, and when present, are responsible for the broad variety of polyketide structures found in dinoflagellates [171]. Traditionally, these enzymes are classified into 3 types, according to their domain organization, in particular Type I PKSs which correspond to large multifunctional enzymes with modular or iterative activity [172, 173].

To date, the transcriptomes of several CTX-producing species of *Gambierdiscus* have been investigated: *G. polynesiensis, G. belizeanus, G. australes* and *G. excentricus* [170, 174, 175] and contigs with sequence similarity to Type I PKSs were found, as reported in other dinoflagellates [171, 176, 177]. Coincidentally, all four species also produce 44-methylgamberione [138, 139]. Of note, no differences have been highlighted in the expression of the monofunctional KS domains between these four species [174], although substantial differences exist in these strains' known toxin profiles for CTXs and MTXs: e.g., at least six P-CTX analogs have been detected in *G. polynesiensis* cultures while three unknown CTXs are suspected in *G. excentricus*; moreover, MTX1 is produced by *G.*

australes vs. MTX2 and MTX4 in *G. excentricus* (Table 2), whereas low amount and no MTXs has been found in *G. polynesiensis* and *G. belizeanus*, respectively (Table 4).

Additionally, contigs with sequence similarity to type II Fatty Acid Synthase (FAS) genes were also found [174]. This differentiation of PKS and FAS pathways in *Gambierdiscus* is important, as it will likely facilitate approaches to investigate toxin biosynthesis pathways in this dinoflagellate.

In summary, the genetic basis of CTXs and MTXs synthesis is still unresolved and additionnal fundamental studies are required to further understand these perplexing pathways, in order to promote the development of novel methods for the monitoring of these harmful dinoflagellates.

5.3.3.2. Growth Stage

An earlier study showed an increase in total toxicity using MBA from the exponential to the stationnay phase for five *G. toxicus* strains originating from the Pacific and the Atlantic Oceans, regardless of N:P ratio [110]. These results are consistent with the common belief that ciguatoxins are secondary metabolites as their production is enhanced during the stationary growth phase. The variability of toxin production in *G. polynesiensis* was also evaluated at different growth stages via the MBA and r-RBA [83]. Regardless of the test used, CTXs production decline from the beginning to the end of the exponential growth phase to 3.4 ± 0.1 eqv P-CTX3C pg.cell^{-1} followed by an increase during the stationary phase up to 11.9 ± 0.4 eqv P-CTX3C pg.cell^{-1} [83]. It is noteworthy that freshly inoculated cells produce also high amounts of CTXs similarly to the ones monitored at the end of the stationary phase. For MTXs production measured by MBA, the same production pattern was observed in *G. polynesiensis* showing a toxicity of 18 ± 4 x10^{-5} MU.1000 cell^{-1} and almost twice during the stationary phase at 31 ± 9 x10^{-5} MU.1000 cell^{-1} reaching a maximum in freshly inoculated cells 50 ± 10 x10^{-5} MU.1000 cell^{-1} [83]. In *G. australes* isolated from the Macaronesian Islands, MTXs were not produced during the exponential phase, but only during the stationary phase [166].

When comparing CTXs and MTXs production in *G. polynesiensis*, the same pattern was observed for both except that CTXs were dominant in aged cells at the end of the stationary phase [83]. This CTXs production pattern was also observed in *in vitro* cultures of *G. toxicus* presenting an increase in toxicity in aged cells [111, 156, 178]. So, if one wants to compare levels of toxin production between several strains of *Gambierdiscus* spp., cells should be cultivated under the same laboratory conditions along with a harvest time at the same growth age. For several *Gambierdiscus* species, cell division seems to be slow down during the stationary phase, but the positive correlation of toxin biosynthesis with aged cells is still unclear [19, 83]. It has been hypothetized that the energy required by *Gambierdiscus,* or other toxic dinoflagellates, can not be allocated at the same time to cell division and toxin production [70, 83, 111, 179]. Additionnally, the high toxin content measured in *G. polynesiensis* was linked to a growth rate slower than for other *Gambierdiscus* species [83] as also observed for *G. excentricus* and *G. carpenteri* [19, 70, 86]. A low growth rate with high production of intracellular toxin could also be considered as a particularly advantageous evolutionary strategy in the natural environment, to improve self-protection in reducing competition with other microalgae or to limit grazing by herbivores [19, 83, 180]. On the contrary, a positive relationship was observed between a high growth rate and "relative" high

levels of CTXs production [0.2 - 0.697] pg P-CTX1B eqv.cell^{-1} during the exponential growth phase in *G. australes* strains originating from Macaronesian Islands [166].

5.3.3.3. Contribution of Bacterial Flora

Previous studies have not found an influence of associated bacteria on CTXs production in *Gambierdiscus* since the toxicity of *Gambierdiscus* strains cultured in axenic vs. xenic conditions were found to be similar, and endosymbiotic bacteria could not be observed in transmission electron microscopy (TEM) sections toxigenic cells [78, 156, 168, 181, 182]. However, a recent study by Wang et al. (2018) [180] has provided evidence that the growth and toxin production of *Gambierdiscus* spp. can be regulated by quorum sensing bacteria. Using nine different co-cultured bacteria, these authors showed that eight of them were able to enhance the growth of *Gambierdiscus* spp., suggesting nutrient supply and/or realease of growth-promoting bioactive substances to this microalgae [180]. Negative and positive interactions on toxin production were also observed, depending on the bacteria co-cultured with *Gambierdiscus* [180]. Different interactions have been suspected between associated bacteria and *Gambierdiscus*: nutrient transferring, sources competition, toxic substance releasing and photosynthesis inhibition that can play a role on algal survival, acquisition of energy, cell division and the ability of *Gambierdiscus* to produce toxins [180]. Then, this algal-bacterial relationship is complex and more efforts should be made in understanding its ecological roles.

5.3.4. Abiotic Factors Influencing Toxin Production in Gambierdiscus and Fukuyoa spp.

From the first studies on *Gambierdiscus* spp., the influence of environmental factors on toxin production was questioned. Because light, temperature, salinity, pH, and nutrients foster the growth and ecological distribution of *Gambierdiscus* dinoflagellates, these factors might also impact toxin production. However, the first attempts to examine CTXs production towards environmental factors were hurdled by unresolved taxonomy in *Gambierdiscus* species [70, 79, 110, 128, 169, 183-186].

Since the 2000s, there has been a globalization of the ciguatera phenomenon due to the geographic extension of *Gambierdiscus* spp. ranges to areas previously spared from this disease (e.g., Europe), probably in response to the effects of climate change [58]. Furthermore, in a global context of climate change, a better knowledge of the environmental factors likely to influence the toxinogenesis of the microalga appears essential if one wants to be able to anticipate the severity of outbreaks varying from one region to another. In this context, the effects of environmental parameters on the growth of several *Gambierdiscus* species have been the subject of recent studies [58, 69, 84, 85, 104, 111]. These studies have shown the ability of some species to adapt to wide ranges of temperature, salinity, light or nutrients and to better understand the geographical distributions of endemic or ubiquitous *Gambierdiscus* species. However, how changes in environmental conditions can affect *Gambierdiscus* toxin production is still explored.

Regarding nutrient parameters, the total toxicity of five *G. toxicus* strains measured by MBA were not significantly influenced by increasing N:P ratio whether during the exponential phase or the stationary phase [110]. Similarly, N:P ratio did not seem to influence Na$^+$ channel activity detected at all N:P ratios for the two toxiest strains MQ2 (Atlantic ocean) and TO4 (Pacific ocean), except at ratio N:P of 5:1 where Na$^+$ channel activity recorded for MQ2 strain was the highest. Conversely, Na$^+$ channel activity was detected for

the three other strains only at the highest N:P ratios [110]. These authors suggested genetic differences between these strains of *G. toxicus* whereas an unresolved taxonomy was probably one of the explanations. CTXs productions of two strains of *G. toxicus* from the Caribean were not affected by organic (nitrate or ammonium) or inorganic (urea, free amino acids or putrescine) nitrogen sources [111]. The only significant effect was observed for one strain whose cells were found to contain higher CTXs levels in the stationary phase vs. the exponential phase when grown on nitrate [111].

When cells were grown at different salinities of 30, 32 and 35, the toxin profile of *G. toxicus* was modified in terms of the ratio of the most abundant CTX putative precursor [128]. In the same way, *G. carpenteri* originating from the Philipines sampled at a salinity of 30, showed a great adaptability in laboratory conditions towards a large range of various salinity levels from 26 to 41 [70]. Within this tolerable range of growth, CTXs production was optimal under the lowest salinity, i.e., 26, showing the highest cellular content of 7.48 ± 0.49 pg PbTx3 eqv.cell^{-1} followed by a decline in CTXs production starting at 29 until the highest levels of salinity tested [70]. How an increase in salinity can actually interfere with toxin biosynthesis is still unexplained. However, a possible explanation could be that the toxins acting on voltage gated sodium channels (activators or inhibitors) produced by these toxic dinoflagellates may affect osmoregulation of ion concentrations inside the cells [187].

The effect of light on *Gambierdiscus* toxins production has also been investigated. As mentioned previously, this dinoflagellate is able to grow in shaded as well as high lighted water habitats [50]. Toxin production in *G. carpenteri* was high at low light conditions and decrease slowly by 2-fold under highest light intensities [70]. Photoinhibition did not seem to occur as toxin production was still maintained under high light intensities [70]. Little is known about the link between photosynthesis and biochemical pathways needed for toxin production in dinoflagellates, although a study has shown that an increase of chlorophyll *a* content following an increase in light intensity was observed in parallel with a decrease of toxin production in *Pyrodinium bahamense* var. *compressum* [188].

When *G. carpenteri* was grown under a wide temperature range of 19-33°C, the highest toxin production was recorded at 19°C followed by a 2-fold decrease and stabilization at 27-33°C [70]. Moreover, when its toxin production declined, an increase in growth rate was observed. It has been speculated that this negative relationship, also observed in other *Gambierdiscus* species and toxic microalgae, may be due to the adverse effects of temperature changes that could influence up and down regulation of mRNA during toxin biosynthesis [70 and reference therein].

5.4. Ecological Relevance of Ciguatera-Related Compounds

The ability of microorganisms to produce and release chemicals/toxins that affect potential competitors for resources is well known among dinoflagellates [189-191]. The diversity and structural complexity of toxins synthesized by epiphytic *Gambierdiscus*/*Fukuyoa* spp. have led to speculation that they may be allelochemic agents directed against co-occurring taxa of the thallisphere [45]. In particular, *Gambierdiscus*/*Fukuyoa* spp. are frequently found associated with other dinoflagellates in the genera *Ostreopsis*, *Prorocentrum*, *Coolia, and Amphidinium* in benthic assemblages of ciguateric biotopes [42, 192, 193]. The allelopathic effects of ciguatera-related toxins towards

these taxa are still poorly documented. Earlier studies showed that *Prorocentrum concavum* and *G. toxicus* were reciprocally inhibited both in exudate-supplemented cultures and in cross-cultures, and that both exudates and CTX extracts of *G. toxicus* were able to inhibit the growth of several diatoms and chlorophytes species [for a review see 194]. A more recent study also showed that, in crossed culturing experiments, culture media preconditioned with filtered-exudates of *G. toxicus* were able to inhibit the growth of *Coolia monotis* and *Ostreopsis lenticularis* [195]. Of note, only one study has addressed the possible role of gambieric acid-A as an endogenous growth enhancer towards *G. toxicus* cultures [196].

Conversely, extracts of several benthic taxa known to co-occur with *Gambierdiscus* spp. in ciguateric biotopes, e.g., *Prorocentrum lima*, *O. lenticularis*, *C. monotis*, are able to suppress *Gambierdiscus* spp. growth or adherence capacity in the laboratory [195, 197, 198]. However, evidence shows that these allelopathic effects may be under the control of various environmental factors such as temperature or salinity (suppression or reversal of the inhibitory effects of *Ostreopsis* sp. on *G. carpenteri* growth) [198].

Since antagonist relationships of *Gambierdiscus* with co-occuring benthic dinoflagellates [17] or diatoms [101] are sometimes observed in the field, it appears interesting to pursue and developp laboratory studies in order to better characterize interspecific interactions among ciguateric phytobenthic communities and to better understand the ecological relevance of the secondary metabolites produced bu *Gambierdiscus*/*Fukuyoa* species. Apart from being used to compete for space, these molecules could also eventually be used to repel grazers or repress the growth of pathogenic organisms. Moreover, to this date, lab-experiments haven't really adressed the characterizations of which secondary metabolites are responsible for these allelopathic effects.

6. SOCIO-ECONOMIC IMPACTS OF CIGUATERA POISONING

Ciguatera Poisoning (CP), associated to CTXs exposure, results in a large declination of gastro-intestinal, cardio-vascular, neurological, neuropsychiatric and other systemic manifestations, which may last weeks, months or even years [9], and is considered the most commonly reported marine biotoxins related illness worldwide, with an annual incidence estimated between 50,000 and 500,000 [199]. CP is also known to be responsible for substantial human health and socio-economic impacts for populations living in endemic regions, especially from the South Pacific, and a threat for millions of costal living inhabitants. Nevertheless, the ability to assess CP socio-economic impacts prone to be challenging due to the lack of i) biological diagnosis tools, that contribute to the difficulty diagnosing CP due to the non-specific nature of symptoms, ii) global awareness, especially among the medical community, iii) specific reporting systems and, iv) systematic ciguatoxic fish screening due to expensive CTXs detection tests.

6.1. Ciguatera Poisoning Impact on Health-Related Expenses

CP incidence is not easy to ascertain because of an important under-reporting in part due to the fact that persons affected often do not seek medical attention, especially in endemic

regions where populations have become accustomed to heal themselves relying on traditional medicines [200, 201], and that health care workers, may have difficulties to correctly diagnose the disease, and if so, do not know or are not obliged to declare cases to authorities. Indeed, CP specific reporting systems are scarce and CP report is mandatory in only few countries (Cayman Islands, Cuba, Miami, Canary Islands, Hong Kong) [202, 203]. This has for consequence that CP under-reporting can rich 90% in some part of the world [204] and contributes to the rarefaction of studies aiming at assessing health-related costs.

Despite these difficulties, some authors estimated individual CP health expenses at USD $1,513/reported case in Cook Islands [205]; USD $1,613/reported case and USD $749/unreported case in Moorea Island (French Polynesia) [206]; USD $1,000/reported case and USD $700/unreported case in developed countries such as Canada [207], USD $545 in US Virgin Islands and USD $200 in Aruba [203]. Global Public health-related costs were grossly estimated at USD $ 19 million/year in USA tropical jurisdictions (Florida, Hawaii, Puerto Rico, Virgin Islands, Guam, American Samoa, Nothern Mariana Islands) for the period 1987-1992 [208] and USD $241,847 for the period of 2007-2013 in Moorea Island (French Polynesia) [206]. Todd (1985) [207] estimated the CP economic impact associated with medical costs and lost-labor productivity for Canada at CAD $2.7 million/year, between 1960's and 1980's. CP economic impacts (including estimated health-related costs, and monitoring and management costs) where estimated around NZD $396,000 in 2011 in Rarotonga (NZD $750,000 during epidemic pick in 2006) [205].

Of note, these estimation were obtained under different contextual circumstances, such as the study period, the level of populations' dependence to marine products, social costume, access to imported food, demographic trends, hospitalization duration or number of days off work, that can interfere in calculations' extrapolation and renders comparisons difficult [54, 92, 209, 210]. It does not take in account either insurance costs purchased by certain seafood companies to cover potential ciguatera-caused damages [211], or direct arrangements for medical expenses reimbursement between seafood sellers and ciguatera affected consumers, as is customary in some Pacific Islands, such as French Polynesia. Moreover, these cost estimations are limited to the acute maganement of CP and exclude the burden of medical expenses related to chronic sequels, that can last for months or even years, and concern over 20% of the population affected [11, 12]. Finally, if CP is retalivelly easy to diagnose in endemic regions, it can prove to be complicated in temperated areas where the diagnosis can take several months, multiple specialists consultations, and expensive medical examinations (blood and urine analysis, electromyogram, scanner, Magnetic Resonance Imaging, biopsies, etc.), whose expenses can significantly weigh the costs associated to patients' management.

6.2. Ciguatera Poisoning Impact on Local Fisheries

Fish contribute substantially to the livelihoods of Pacific Islands Countries and Territories (PICTs) nations whose annual fish consumption rate are among the highest in the world (between 50 to 110 kg/capita) [212]. Besides providing Pacific islanders with essential dietary proteins and animal fat, marine products also represent an important mainstay for local economies in that they contribute significantly to households incomes [213, 214]. CP therefore represents a major concern and burden for these communities and fisheries industry [215]. Of note, fish species commonly regarded as ciguatoxic fish, such as groupers,

snappers, mackerels, jacks, barracudas, wrasses, parrot fish and surgeon fish, are often listed among the main species sold in many market places [9, 216].

In the Cook Islands, the increase of CP occurrence over the past two decades has progressively discouraged local fish consumption [2]. Indeed, results of a survey realized in 2006 indicated a constant decline in average daily *per capita* fish consumption rates since 1989, from 318 g in 1989 to 176 g in 2006. These results are in accordance with observations made in Tuvalu, especially in Funafuti, where the number of fish species affected by ciguatera has increased concurrently with the risk of discouraging consumers to eat marine products [217].

In the absence of global consensus and systematic CTXs detection in marine products, health autorities from endemic regions usually put bans on ciguatera emblematic species, or specimens over a certain size, based on the general assumption that a positive correlation exists between the amount of toxins and fish size. Such regulation exists since 1939 in French Polynesia and has progressively be implemented in American Samoa, Fiji, Hawaii, New Zealand, Australia, Florida, Mexico, Cuba, Puerto Rico, Gualeloupe, Reunion Islands, etc., with, nevertheless, some variations in species listed from a country to another [203, 218-222]. Some countries, such as the Dominican Republic, have also opted for temporal restrictions since they recommend avoiding certain at-risk species between the months of May and August [203].

The economic losses caused by the harvest loss associated with these restrictions have been tentatively estimated around USD $1.1 million/year in French Polynesia [223], USD $10 millions in Caribbean [199] and over NZD $700,000 during CP epidemic in Cook Islands according to Rongo and van Woesik (2012) [205].

6.3. Ciguatera Poisoning Impact on International Trade

A typical example of how a single-CP event can lead to the permanent closure of an export industry is the one of the Republic of Kiribati, where fish trade used to be an important source of income for local fishermen (estimated over AUD $8,000/fisherman). In 1999, a major CP outbreak occurred in Hong Kong with fish supposedly imported from Kiribati. This event resulted in the ban of all fish from Kiribati in the Hong Kong market, and in the total closure of the trade in Kiribati, which represented an annual revenue loss of AUD $250,000 [224].

CP cases reported these past nine years in Europe by the European Rapid Alert System for Food and Feed (RASFF) where all due to fish imported mainly from Indian Ocean and South-East Asia [225].

Given that many countries do not have laboratory CTXs detection capabilities, and lack accurate species labelling and traceability procedures, and that no regulatory limits nor reference methods exist, regulation policies regarding the trade of potential ciguatoxic fish relies entirely on the appreciation of local authorities. Based on the understanding that fish are not screened on a routine basis, recommendations, mostly concern the avoidance or prohibition of specimens, particularly large predatory reef-fish that are regarded as "suspect" simply because they originate from affected areas [209].

The Council Directive 91/493/EEC of the European Community states that placing on the market "*fishery products containing biotoxins such as ciguatera toxins or muscle-paralysing toxins*" is forbidden [226], while in its Guidance for industry, the US-Food and Drug Administration (FDA) recommends that "*because ciguatoxic endemic areas are localized, primary seafood processors should recognize and avoid purchasing fish from established and emerging areas of concern*" [227].

Alternatively, other countries such as Australia (Sydney Fish Market) may choose to circumscribe the field of restrictions, by publishing several lists of bans based on different criteria: i) a list of prohibited specific species whatever their origin (chinaman or chinaman snapper, tripletail maori wrasse, humpback maori wrasse, red bass, paddle-tail or humped-back red snapper and moray eel); ii) a list of prohibited specific species from precise locations (coral trout form Fijian waters); iii) a list of prohibited locations whatever the species (Kiribati or Marshall Islands); and iv) a list of species maximum size limits [228].

6.4. Ciguatera Poisoning Impact on Tourism

Globally, travelers are poorly informed about ciguatoxic risk by the tourism industry. According to the United Nations World Tourism Organization, there were over 1.3 billion "international tourist arrivals" in 2017. This data is in constant augmentation since 2010 [229], like the risk of contracting uncommon pathologies, such as ciguatera, for a temperate region traveler due to tourist attractiveness for tropical and subtropical countries [230, 231].

Some countries show a certain reluctance to communicate on their ciguatera incidence for fear of a dramatic decrease in tourist frequentation. In at-risk areas, CP has been associated to a decrease in tourism and recreational fishing [209, 211] and represents a constent source of apprehension to hotels and restaurants industry. Indeed, if a severe poisoning event should occur, this could derive to a loss of business and a long-term stigmatization of the establishment.

In 2019, 55 countries and island territories were listed as "at-risk destinations" by the International Association for Medical Assistance to Travellers (IAMAT) [232]. For countries regarded as at high risk of ciguatera, the extent to which this ciguatoxic status may actually influence the choice of it as a travel destination in tourists' mind is not documented, as yet.

6.5. Ciguatera Poisoning as a Cause of Lifestyle and Tradition Upheaval

It has been suggested that CP have impacted human migration, and fishing and dietary patterns among Pacific populations [2, 209, 233, 234].

Beyond its direct impact on fisheries, ciguatera can also lead to drastic changes in lifestyle linked to a progressive loss of food capital [204] and a forced dietary shift among local populations, resulting in a strong reliance on imported and/or canned products, with the risk of increasing sugar and fat intake. As an example, a shift in dietary habits was reported among Rarotonga residents (Cook Islands) who modified their fish consumption in favor of an increased intake of chicken and canned fish, particularly during the peak of a ciguatera outbreak [2]. Moreover, some PICTs not only observed changes in their population's diet, but

also reported secondary medical consequences, such as diabetes, as an indirect aftermath of CP [214].

Finally, a survey conducted among Rarotonga communities showed that CP may also interfere and disrupt the intergenerational transmission of traditional knowledge in affected communities, particularly with regard to fishing practices [205].

6.6. Ciguatera Poiosning before the Law

With increasing CP incidence, not only appeared a loss in confidence of consumers regarding fishery industry, but also legal actions for non-compliance with regulations or requests for compensation. An example of litigation concerned a CP event involving 46 individuals attending a banquet at a restaurant, which served maori wrasse fish imported from Trunk Reef in Queensland (Australia), in 1997 [235]. One of the affected consumers made a legal claim against the restaurant, which turned against the fish supplier. As a result, both the restaurant and the supplier were declared negligent by the judge in charge [236]. In the coming years, it is expected to assist to an increase of lawsuits of this type.

According to the Food and Agriculture Organization (FAO) of the United Nations "*ciguatera dinoflagellates are predicted to become one of the increasing food safety threats due to climate change*" [237], so that a significant increase in ciguatera burden is to be expected, not only in endemic regions, but also at a global scale. The multiple ramifications of ciguatera thus emphasize the need for more thorough studies using a more integrated approach of CP socio-economic impacts, for improved ciguatoxic risk prevention and management.

CONCLUSION

Significant advances have been achieved in the past two decades in the understanding of the ciguatera dinoflagellates *Gambierdiscus* and *Fukuyoa*. Still, ciguatera events occurence and variability in their severity across geography remain difficult to predict.

Identifying the key-factors likely to contribute to ciguatera flare-ups is very challenging due to the multitude of potential influential factors and their interactions. Although much of the data available in the early work on *Gambierdiscus* spp. is valid for the genus, many studies will have to be redone for the various species now known to exist in *Gambierdiscus* and *Fukuyoa* genera. Too, in laboratory-based studies, experiments designed to explore the concomitant effects of two or more factors on *Gambierdiscus*/*Fukuyoa* spp. growth should be encouraged, since responses may significantly differ from those obtained in single-factor studies. Moreover, the current knowledge on these organisms needs to be reassessed through more observational field studies since natural conditions often produce responses that are different from laboratory-controlled conditions.

Furthermore, most of the studies currently available in the literature were designed to assess inter-specific variability based on the growth response of a single strain for each species, but little is known about the intra-specific variance within each species. Some authors have speculated that isolates within a given species can easily adapt to the changes of

environmental conditions, and that the differences observed in growth responses and toxin production between isolates at varying environmental conditions may be habitat dependent rather than species dependent [70, 198]. This has prompted recent studies aiming at investigating the effect of fine-scale habitat heterogeneity (e.g., macroalgal cover, composition of epiphytic communities, etc.) on the dynamics of benthic harmful dinoflagellate assemblages, including *Gambierdiscus* spp. [193].

Gambierdiscus/*Fukuyoa* communities in a given area can comprise multiple co-occuring species that vary with respect to their toxicity. Therefore, species composition of blooms and most importantly the presence of certain highly toxic species and/or strains are likely to play a prominent role in both CFP flare-ups and severity of outbreaks [4, 17, 19]. It is thus of utmost importance to devote future research efforts to: i) fully characterize the toxin profile associated with each of the species and genotypes now known, focusing primarily on species known to produce substantial amounts of toxins, particularly *G. polynesiensis*, and *G. excentricus*; ii) clarify how these algal toxin profiles may contribute to shape the toxin profiles in ciguatoxic fish, and iii) clarify the biological activities and contribution of recently characterized compounds in ciguatera symptomatology. All these data will be useful to inform ciguatera risk models.

Future field ecology studies should also examine the role of the macroalgal community in the transfer of ciguatera toxins to higher trophic levels, particularly with regard to how algal palatability and grazing pressure from herbivores can significantly influence toxin flux injected in marine food webs [105].

Finally, field observations are increasingly showing that other epiphytic dinoflagellates often co-habit with *Gambierdiscus*/*Fukuyoa* communities in benthic assemblages of ciguatera-prone biotopes [42, 92, 192]. These benthic HAB species are known to be the potential source of other potent toxins likely to bio-accumulate in marine food webs, and whose potential contribution to ciguatera symptomatology is still poorly documented. In this regard, the introduction of high throughput screening techniques such as metabarcoding in current monitoring programs would greatly benefit this area of research.

Undoubtedly, the greatest challenge for the ciguatera scientific community in the coming years will be to translate the recent advances in the knowledge-base of the ecology and toxicology of *Gambierdiscus*/*Fukuyoa* spp. into practical solutions for a more reliable assessment of ciguatera risk and effective mitigation programs.

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