# Dinoflagellate Phycotoxins

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Dinoflagellates are single-celled eukaryotes constitute an important group of phytoplanktons, characterized by two dissimilar flagella and distinctive features of both plants and animals.

Keywords: harmful algal bloom ; dinoflagellate ; phycotoxin ; algae ; metabolite ; toxin ; toxicity

## 1. Introduction

Microalgae are photosynthetic microorganisms belonging to diverse phyla [1]. Over the past few decades, several green microalgae, such as *Chlorella* spp., *Scenedesmus* spp., and *Dunaliella* spp., have been recognized as useful bioresources for producing commercial materials, namely cosmetics, pharmaceuticals, dietary supplements, biofuels, and biofertilizers [2][3][4][5][6][7]. In contrast, phycotoxin-producing cyanobacteria, dinoflagellates, and raphidophytes are known to generate frequent harmful algal blooms (HABs), thereby causing severe losses to the fishing industry and aquatic ecosystem [8][9][10][11]. For instance, Lake Erie in the United States is a well-recognized recreational place, but the ecosystem services are under threat owing to cyanobacterial-generated HABs. The annual economic loss of fishing expenditures in Lake Erie was estimated to be approximately USD 2.25–5.58 million during bloom formation [12]. Additionally, massive HABs caused by the dinoflagellate *Karenia mikimotoi* resulted in a mass mortality of abalones, with a loss of over USD 290 million in China [11].

Several factors that cause the death of aquatic organisms have been reported, including direct reactive oxygen species production, phycotoxins, and bioactive fatty acids generation [13]. For instance, the raphidophyte *Chattonella marina* produces superoxide anion via an NAD(P)H oxidase-related mechanism [14], and cyanobacterial species, including *Anabaena* spp. and *Microcystis* spp., produce cellular microcystin, which has previously demonstrated human hepatotoxicity via bioaccumulation in the food chain [15]. Among the algal taxa, dinoflagellate is considered a major HAB-forming group, which causes red tide in coastal areas. Many dinoflagellate species show a mixotrophic nature, practicing both photosynthesis and prey ingestion simultaneously [16]. Furthermore, many species produce phycotoxins, such as saxitoxins (STXs), hemolysins (HL), and yessotoxins (YTX), which exhibit intrinsic modes of action. Although managing and monitoring dinoflagellates has been under the spotlight for the past few decades, industrial applications of phycotoxins have not garnered much attention.

## 2. Effects of HABs Produced by Dinoflagellates

Dinoflagellates are unicellular eukaryotes belonging to phylum Dinoflagellata. Many of its species cause red tide in coastal areas, which significantly damages aquatic life and causes paralytic shellfish poisoning (PSP), neurotoxic shellfish poisoning (NSP), diarrhetic shellfish poisoning (DSP), and ciguatera in humans worldwide [10][11][17][18][19][20]. There are more than 2000 identified dinoflagellate species, and they exhibit distinct characteristics, including those of the autotrophs, heterotrophs, and mixotrophs [21]. Morphological characteristics of dinoflagellates include two dissimilar flagella arising from the ventral cell side. These organisms are capable of producing diverse phycotoxins and render HAB-derived damage [22]. During the 1990s, *Cochlodinium* spp. (mostly *C. polykrikoides* and *C. fulvescens*) caused damage to the fishing industry with an estimated annual loss of more than USD 100 million in South Korea [23][24]. Out of these, *C. polykrikoides* caused an economic loss of approximately USD 69.5 million in 1995. Moreover, a massive bloom of the dinoflagellate *Karlodinium digitatum* caused approximately USD 32 million damage to the fishing industry of Hong Kong [11]. Additionally, *K. mikimotoi* caused a massive economic detriment of more than USD 290 million to the fishing industry in China in 2012 [11].

Harmful effects of dinoflagellate-generated HABs associated with other organisms have been extensively investigated over the past few decades. For instance, Chen et al. reported that a polar lipid-soluble component derived from *K. mikimotoi* extract inhibited proliferation, disrupted cell membrane, and increased lipid peroxidation (increased

malondialdehyde content) in mammalian cells [25]. Further, the addition of *K. concordia* extract induced anesthesia in brine shrimp [26] and the PSP (e.g., STX)-producing *Alexandrium fundyense* consumed by copepods was lethal to fish [27].

However, biotoxins derived from diverse organisms have potential applications. In particular, botulinum toxin produced by the bacterium *Clostridium botulinum* is widely used for the treatment of migraine headaches, muscle spasticity, and other muscle disorders [28][29][30]. Additionally, pufferfish-derived tetrodotoxin is therapeutically used to manage acute heroin withdrawal syndrome and alleviate cancer pain [31][32]. These biotoxins have specific modes of action, and they have potential and extensive industrial applications. Although a lot of phycotoxins derived from dinoflagellates have been extensively studied, their industrial application based on their specific modes of action is still poorly understood.

## 3. Dinoflagellate Phycotoxins and Their Modes of Action

Table 1 summarizes the reported dinoflagellate-produced phycotoxins. *Alexandrium* spp. are considered PSP-producing harmful organisms. The causative paralytic toxins of *Alexandrium* spp. include STX, gonyautoxin (GTX), neosaxitoxin (NSTX), and HL [33][34][35][36]. Among these, STXs are well-known marine algal toxins that block the cellular sodium channel. STX is included in the guanidinium neurotoxin group, sharing the common chemical feature of guanidinium moieties and interacting with voltage-gated sodium channels with high binding affinity and ion flux blockage capacity. This blockage induces the reduced influx of $Na^+$ ions into a cell and causes inhibition of the propagation of action potentials in excitable membranes. This process ultimately induces neuromuscular paralysis [37]. The symptoms of PSP induced by STX and its analogue, NSTX, include numbness of the lips and gastrointestinal disorders [35]. Lefebvre et al. [34] reported that measurable levels of STX were detected in both field and cultured *Alexandrium* spp. using a receptor-binding assay and enzyme-linked immunosorbent assay. The structure and analogues of STX were previously well-described by Wiese et al. [38]. *Gymnodinium catenatum* and *Pyrodinium bahamense* produce STXs as well [39][40]. Landsberg et al. [40] reported that the source of STXs detected in pufferfish skin, muscle, and viscera was putatively derived from *P. bahamense*. In addition, Sako et al. [39] purified and characterized sulfotransferase-specific STX analogues from the cytosolic fraction of *G. catenatum*. GTXs influence the mammalian nervous system by binding to site 1 of the α-subunit of the voltage-dependent sodium channel in the postsynaptic membrane, thereby preventing synaptic function [41].

**Table 1.** List of phycotoxins derived from diverse dinoflagellates and their modes of action.

| Dinoflagellate | Toxins | Mode of Action | References |
|---|---|---|---|
| ***Alexandrium* spp.** | **Saxitoxin (STX)** | **Inhibits sodium channel** | [34][35] |
| | **Gonyautoxin (GTX)** | **Inhibits sodium channel** | [33][35][36] |
| | **Neosaxitoxin (NSTX)** | **Inhibits sodium channel** | [35][36] |
| | **Haemolysin (HL)** | **Hydrolyses phospholipids in the bilayer**<br>**Form pores in phospholipid bilayers** | [36][42] |
| ***Amphidinium carterae*** | **Haemolysin (HL)** | **Hydrolyses phospholipids in the bilayer**<br>**Forms pores in phospholipid bilayers** | [33][36] |
| ***Azadinium spinosum*** | **Azaspiracids (AZA)** | **Blocks hERG (human ether-a-go-go related gene) potassium channel by binding to it** | [43] |
| ***Cochlodinium polykrikoides*** | **Haemolysin (HL)** | **Hydrolyses phospholipids in the bilayer**<br>**Forms pores in phospholipid bilayers** | [36][44][45] |
| ***Coolia* spp.** | **Cooliatoxin (CTX)** | **Blocks unmyelinated nerves** | [36][46] |
| | **Yessotoxin (YTX)** | **Activates calcium channel**<br>**Decreases cytosolic 3′,5′-cyclic adenosine monophosphate (cAMP) levels** | [47][48][49][50] |

| Dinoflagellate | Toxins | Mode of Action | References |
|---|---|---|---|
| *Dinophysis* spp. | Okadaic acid (OA) | Inhibits protein phosphatases (serine/threonine phosphatases) | [51][52][53][54][55] |
| | Dinophysistoxin (DPX) | Inhibits protein phosphatases (serine/threonine phosphatases) | [56] |
| | Pectenotoxin (PTX) | Inhibits protein phosphatases (serine/threonine phosphatases)<br>Depolymerizes actin filaments<br>Disrupts actin cytoskeleton | [35][57][58][59] |
| *Gambierdiscus toxicus* | Maitotoxin (MTX) | Activates calcium channel | [60] |
| *Gonyaulax* spp. | Haemolysin (HL) | Hydrolyses phospholipids in the bilayer<br>Forms pores in phospholipid bilayers | [46] |
| | Yessotoxin (YTX) | Activates calcium channel<br>Decreases cytosolic 3′,5′-cyclic adenosine monophosphate (cAMP) levels | [49][50][61] |
| *Gymnodinium catenatum* | Saxitoxin (STX) | Inhibits sodium channel | [39] |
| *Heterocapsa circularisquama* | Haemolysin (HL) | Hydrolyses phospholipids in the bilayer<br>Forms pores in phospholipid bilayers | [48] |
| *Karlodinium* spp. | Karmitoxin (KTX) | Unknown (Ichthyotoxic) | [62][63] |
| | Karlotoxin (KmTx) | Disrupts cell membrane by specific binding to cholesterol | [63][64] |
| *Karenia mikimotoi* | Brevetoxin (PbTx) | Activates voltage-gated sodium channels | [20][65][66] |
| | Gymnocin (GC) | Unknown | [67][68] |
| | Haemolysin (HL) | Hydrolyses phospholipids in the bilayer<br>Forms pores in phospholipid bilayers | [69] |
| *Lingulodinium polyedrum* | Yessotoxin (YTX) | Activates calcium channel<br>Decreases cytosolic 3′,5′-cyclic adenosine monophosphate (cAMP) levels | [49][50][70] |
| *Ostreopsis* spp. | Palytoxin (PLTX) | Turns Na+/K+ pump into a shape that allows the passive transport of sodium and potassium ions | [36][71][72] |
| *Prorocentrum* spp. | Okadaic acid (OA) | Inhibits protein phosphatases (serine/threonine phosphatases)<br>Depolymerizes actin filaments<br>Induces apoptosis through suppression of the nuclear factor ĸB signaling pathway | [35][36][73] |
| | Dinophysistoxin (DPX) | Inhibits protein phosphatase | [56][74] |
| | Prorocentrolides (PC) | Acts on nicotinic acetylcholine receptors (nAChRs) | [75] |
| | Borbotoxin (BTX) | Blocks postsynaptic nAChRs | [76] |
| *Protoceratium reticulatum* | Yessotoxin (YTX) | Activates calcium channel<br>Decreases cytosolic adenosine 3′,5′-cyclic monophosphate (cAMP) levels | [49][70] |
| *Pyrodinium bahamense* | Saxitoxin (STX) | Blocks sodium channel | [40] |

Altered hemolytic activity of *A. peruvianum* under different nutrient ratios indicated the presence of cellular HL [42]. Although the modes of action of dinoflagellate HL are poorly understood and algal species-specific, a possible mechanism could be the hydrolysis of phospholipids and subsequent pore formation in phospholipid bilayers, a mechanism similar to other hemolytic toxins [77][78]. Modes of action of HLs detected in *Amphidinium carterae*, *C. polykrikoides*, *Heterocapsa circularisquama*, *K. mikimotoi*, and *Gonyaulax monilata* are described briefly in Table 1 [77][78][77][78].

*Azadinium spinosum* produces azaspiracids (AZA), a group of toxic lipophilic polyether compounds. This toxin caused human intoxication symptoms, such as nausea, vomiting, severe diarrhea, and stomach cramps in a study conducted in the Netherlands [43][79]. AZA was originally believed to be a toxic compound produced by *Protoperidinium crassipes* [80]. However, it was later demonstrated that the toxins in *P. crassipes* were a consequence of its feeding on the dinoflagellate *A. spinosum*, which was in turn reported to be the source of the AZA [81]. This toxin causes damage to the intestinal epithelium, lamina propria, liver, and villi as an acute toxic effect, and causes lung tumors and malignant lymphomas at high concentrations with long-term exposure [82][83][84]. AZAs include more than 30 analogues, and among these, only AZA1, AZA2, and AZA3 are currently regulated in edible shellfish by the European Union through their toxic equivalency factors (TEFs) [85]. It exhibited its action by blocking the human ether-a-go-go-related gene (hERG) potassium channel [86]. AZA interacts with the channel's central pore (F656) within the S6 transmembrane domain and physically blocks the potassium-conductance pathway of the hERG1 channels [86]. Pelin et al. [87] previously reported that the exposure of immortalized human hepatocyte (IHH) cell line to AZA analogues induced mitochondrial electron transport chain complex-dependent mitochondrial dehydrogenases activity (MDA) in a concentration-dependent manner. The MDA was suppressed in the $K^+$, $Cl^-$, and $Na^+$ free media, and by specific inhibitors of $K_{ATP}$ (glibenclamide), hERG potassium channels (cisapride), $Na^+/K^+$, ATPase (ouabain), and cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels (CFTR(*inh*)-172). These results revealed that the AZA-induced MDA is derived from an imbalance of intracellular levels of $K^+$ and $Cl^-$ ions [87]. The toxic effects, structure, and analogues of AZA were well-described in previous studies [79][88][89][90][91][92].

Another dinoflagellate genus, *Coolia*, produces cooliatoxin (CTX) and YTX [46][47]. Holmes et al. [46] purified a novel toxin from *C. monotis* isolated from Australia and named it CTX. This toxin is considered a monosulfate polyether analogue of YTX and caused initial blockage of unmyelinated nerves in vitro, as reported by Holmes et al. [46]. Additionally, sulfated polyether analogues of YTX have been detected in *C. malayensis* through chemical analysis using NanoLiquid chromatography–mass spectrometry [47]. YTX is a diarrhea-causing toxin and exhibits its toxicity by activating nifedipine and the SKF-96365 sensitive calcium channel [49], and by decreasing cytosolic 3′,5′-cyclic adenosine monophosphate (cAMP) levels [50]. YTX-producing dinoflagellates include *Gonyaulax spinifera*, *Lingulodinium polyedrum*, and *Protoceratium reticulatum* [61][70]. The structure and analogues of YTX were previously well-described by Paz et al. [93].

*Karlodinium armiger* produces karmitoxin (KTX), which is an amine-containing polyhydroxy-polyene toxin [63]. Although its specific mode of action is not yet identified, ichthyotoxic effects of this toxin toward fish larvae and juveniles have been demonstrated recently [94]. The structure of KTX was previously reported by Rasmussen et al. [63]. Additionally, *Karlodinium* spp. produces karlotoxin (KmTx), which is structurally similar to amphidinols and is the causative toxin for membrane permeabilization [64]. KmTx is produced by *K. armiger* and *K. veneficum*, and its mode of mechanism is the disruption of the cell membrane by specifically binding to cholesterol [63]. The structure and several analogues of KmTx were reported by Van Wagoner et al. [95].

*Dinophysis* is a medium-sized dinoflagellate that produces DSP toxins, including okadaic acid (OA), pectenotoxin (PTX), and dinophysistoxin (DPX) [36][54]. OA is a polyether fatty acid, and its structure is highly similar to that of acanthifolicin [52]. DPXs are considered analogues of OA, whereas PTXs are a type of polyether lactones [96][97]. The mode of action of OA and DPXs is an inhibition of the serine/threonine (Ser/Thr) phosphatases that further induces tumor growth promotion and neuronal cell death [52][53][98][99]. The structures and analogues of OA and DPX were previously reported by Uchida et al. [100] and Fernandez et al. [101]. PTXs demonstrate diverse physiological functions, including inhibiting Ser/Thr phosphatases, depolymerizing actin filaments, and disrupting the actin cytoskeleton [35][36][57][58][59]. According to Espiña et al. [102], marked depolymerization of F-actin, associated with an improved G-actin level in hepatocyte cell line by PTX-1, PTX-2, and PTX-11 (1–1000 nM) treatments, was observed via confocal image analysis. However, no activity was observed by treatment with PTX-2 seco acid (PTX-2 SA), which is an enzymatically digested derivative of PTX-2 [102]. PTXs were initially classified into the DSP-producing group; however, mice toxicity tests confirmed that this toxin does not induce diarrheic symptoms but causes severe hepatotoxicity [103]. Specifically, Miles et al. [104] previously developed an effective method to isolate pectenotoxins from dinoflagellate cells, and they showed isolated PTX-2 caused acute toxicity in mice, whereas its derivative, PTX-2 SA, had no effect at 5000 µg/kg. Additionally, no diarrhea was observed in mice receiving either PTX-2 or PTX-2 SA treatments [104]. The structures and analogues of PTXs were previously described by Allingham et al. [57] and Wilkins et al. [105]. OA can be produced by dinoflagellates *D. acuta*, *D. acuminate*, *D. fortii*,

*Prorocentrum concavum*, *P. rhathymum*, *P. belizeanum*, *P. lima*, and *P. arenarium* [106][107][108][109]. DPXs are produced by *D. acuta*, *D. acuminate*, *P. foraminosum*, and *P. lima* [74][110][111][112], whereas PTXs are produced by *D. fortii*, *D. acuta*, *D. acuminate*, and *D. caudata* [109][113][114].

*Gambierdiscus toxicus* produces ciguatera-inducing maitotoxin (MTX) [115]. Holmes and Lewisk purified *G. toxicus*-derived distinct MTXs using high-pressure liquid chromatography and reported that these compounds caused contractile responses of the muscle [105]. MTX is considered one of the largest natural products (3422 Da) that can activate cellular calcium channels [60][116]. Takahashi et al. [60] showed the association of increased calcium influx and calcium-dependent release of [3H] norepinephrine in a pheochromocytoma cell line. Their findings indicated that MTX's mode of action is the activation of cellular calcium channels. The structures and analogues were previously described by Reyes et al. [117].

*Karenia* spp. dinoflagellates, including *K. brevis* and *K. mikimotoi*, are well-recognized as harmful algae in Japan and the USA [110][111]; these species produce brevetoxin (PbTx) and gymnocin (GC), respectively [66][67][68]. PbTx activates mammalian voltage-gated sodium channels, thereby causing NSP [20][65][118]. Further, aerosolized PbTx in sea spray causes reduced respiratory function and asthma [113]. The structures, analogues, and toxicity of PbTx were previously well-elucidated by European Food Safety Authority (EFSA) panels [119]. GCs are polyether toxins that include GC-A and GC-B [67][68]. Although their modes of action are still poorly understood, GCs are carboxylic acids and show moderate cytotoxicity activity against mouse lymphoid P388 cells [67][68]. The structures of GC-A and gymnocin-B were determined by Satake et al. [67][120]. Additionally, Tanaka et al. [68] determined the structures of GC analogues, including GC-A carboxylic acid and GC-A2.

*Ostreopsis* spp. are well-recognized, harmful algae worldwide due to their spread to many tropical and temperate regions. They produce aerosolized palytoxin (PLTX) along with its analogues, which have caused myalgia, respiratory problems, impairment of the neuromuscular apparatus, and abnormalities in cardiac function [121][122]. PLTX is considered one of the most lethal marine toxins, and its mode of action is unique wherein it causes the $Na^+/K^+$ pump to turn into a shape that allows the passive transport of sodium and potassium ions [35][72]. PLTXs and their analogues can be produced by the dinoflagellates *O. siamensis*, *O. ovata,* and *O. mascarenensis* [123][124][125]. The structure, analogues, and toxicity of PLTXs were previously represented by Ramos and Vasconcelos [126].

*Prorocentrum* spp. produce species-specific diverse phycotoxins, such as OA, DPX, prorocentrolides (PC), and borbotoxin (BTX) (Table 1). PCs are a member of the cyclic imine phycotoxins family produced by *P. lima* and *P. maculosum*, and they act on both muscle and neuronal nicotinic acetylcholine receptors (nAChRs) [75][127][128]. *P. borbonicum* produces BTX-A that was purified by Ten-Hage et al. [76] and has a similar mode of action on nAChRs. The general structure, analogues, and modes of action of PCs and BTX were reported by Amar et al. [75] and Ten-Hage et al. [76].

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