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Review

Cyanobacterial Blooms and Their Implications in the Changing Environment

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Abstract

Cyanobacteria are the most ancient phytoplankton that first appeared at least 2.5 billion years ago and have a prolonged evolutionary history. They can form impenetrable and toxic blooms in aquatic ecosystems such as freshwater and marine environments. Cyanobacterial blooms produce cyanotoxins that endanger ecosystem functioning and deteriorate water quality used for recreation, drinking, and in fisheries, thus, adversely affecting human health and the economy. Some bloom-producing genera are *Aphanizomenon, Planktothrix, Cylindrospermopsis, Nodularia, Trichodesmium, Dolichospermum*, and *Microcystis*. They increase turbidity and suppress submerged aquatic vegetation. Due to the microbial bloom-mediated environmental degradation, oxygen scarcity might occur, inducing hypoxia and anoxia, and resulting in the death of fish and benthic invertebrates. Several cyanotoxins cause many diseases related to digestion, liver, and neurological disorders when ingested by birds and mammals, including humans. Global changes resulting from human impacts like eutrophication, rising CO_2 levels, and global warming are major driving forces for the

enhancement of cyanobacterial blooms in many aquatic systems worldwide. Various management strategies such as nutrient load reduction, hydrodynamic changes, and chemical and biological controls have been used to reduce bloom occurrence and proliferation of cyanobacteria. In this chapter, we have discussed the approaches regarding the understanding of how global changes affect cyanobacterial blooms and also suggested effective prediction and management strategies.

Keywords
Cyanobacterial blooms; climate change; eutrophication; management strategies

1. Introduction

The occurrence and potency of cyanobacterial blooms and economic losses related to these events have increased in both freshwater and marine ecosystems [1]. Cyanobacterial blooms can severely affect water quality. They enhance turbidity and strangulate submerged aquatic vegetation [2]. Cyanobacterial blooms deplete oxygen, resulting in hypoxia and anoxia, causing the death of fish and benthic invertebrates. They also alter the nutrient biogeochemistry of water bodies and affect the diversity and abundance of other species. Various compounds related to taste and odor are produced by cyanobacteria, which affect the recreational functions of lakes and drinking water reservoirs. A high concentration of cyanotoxins is also produced, which cause diseases related to liver, digestive, and neurological disorders when consumed by birds and mammals, including humans [3, 4].

The factors responsible for the increase in these cyanobacterial blooms include an increase in nutrient inputs, CO_2 levels, global warming, the transfer of cells or cysts *via* human activities, and the enhancement of aquaculture production or overfishing, which can alter food webs and enable the growth of harmful species [1]. Cyanobacterial blooms increase water temperatures by absorbing excessive light using their photoprotective and photosynthetic pigments [5]. The increase in surface water temperatures resulting from changing global climate may promote cyanobacterial blooms [6]. Cyanobacterial blooms are caused by multiple factors [1]. Blooms caused by the enormous growth of certain cyanobacteria, followed by the production of toxic compounds, occur in eutrophic to hypertrophic lakes, ponds, and rivers around the world [7].

Several toxic compounds (cyanotoxins) are produced by cyanobacteria that occur in freshwater and marine ecosystems [7]. These toxic compounds have many harmful effects on aquatic organisms, animals, and humans. The toxicity of different cyanotoxins depends on cyanobacterial growth and the extent of their toxin production [3, 7]. Different abiotic factors, including light intensity, temperature, pH, and nutrients, determine the growth of different cyanobacteria and their ability to produce toxins [7-9]. Cyanotoxins play an important role in chemical defense, providing survival advantages to the cyanobacteria over other microbes or deterring predators. Cyanotoxins may also participate in chemical signaling.

Cyanotoxins pose risks to human and animal health. Depending on the concentration in the aquatic environment, they can cause severe poisoning, produce chronic diseases such as cancer, and even cause death. There are many groups of cyanobacterial neurotoxins, classified according

to their structure, including alkaloids (anatoxin-a, homoanatoxin-a, and saxitoxins), non-proteinogenic amino acids, e.g., BMAA and the phosphate ester, and anatoxin-a(s). Cyanotoxin hepatotoxicity causes inhibition of serine/threonine protein phosphatases and affects the regulation of cellular protein hyperphosphorylation [10]. Neurotoxicity results in neuromuscular blockade [11], anti-acetylcholinesterase activity, anti-phosphatase activity, postsynaptic cholinergic agonist activity, and also affects protein kinase C activators.

2. Cyanotoxins

Bloom-forming cyanobacteria produce different secondary metabolites, and most of them are toxic to plants, lower animals, and humans at naturally occurring concentrations [4]. Some bloom-forming cyanobacteria such as *Microcystis aeruginosa*, *Merismopedia* sp., *Anabaenopsis* sp., *Anabaena* sp., and *Oscillatoria* sp. from different water reservoirs in Varanasi, India are shown in Figure 1 [12, 13]. Cyanobacterial blooms contain both toxic and non-toxic strains. Therefore, the toxin content and the toxin composition of cyanobacterial blooms depend on the composition of the strain [14]. Cyanobacterial blooms degrade water quality, deteriorate ecosystem stability, and adversely affect human health by producing cyanotoxins in potable, fishable, and recreational water sources. The concentration and types of toxins are highly dependent on the interactions between environmental factors (e.g., light, temperature, pH, nutrient and CO_2 availability etc.) which can promote the expression of toxin genes and toxigenic genotypes [15, 16]. Cyanobacteria, and the toxins released by them, disturb the zooplankton (cladocerans and rotifers) population structure, which can alter ecological processes [17]. Due to cyanobacterial blooms, *Daphnia* populations may decrease when other food sources are depleted. Different species of *Daphnia,* such as *D. pulicaria* and *D. pulex*, can grow in the presence of some toxic cells [18], which affects the dynamics of the zooplankton population. Cyanobacterial toxins can be classified based on their chemical structures, such as cyclic peptides (microcystin and nodularin), alkaloids (anatoxin-a, anatoxin-a(s), saxitoxin, cylindrospermopsin, aplysiatoxins, lyngbyatoxin-a), and lipopolysaccharides (Table 1). Most cyanotoxins are neurotoxins or hepatotoxins [19].

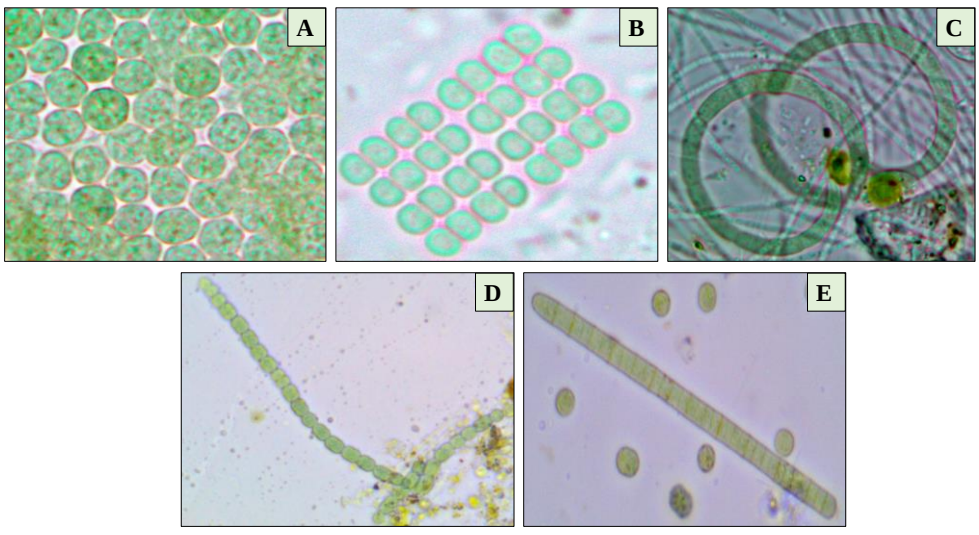

Figure 1 Bloom-forming cyanobacteria from different reservoirs in Varanasi, India. (A) *Microcystis aeruginosa*, (B) *Merismopedia* sp., (C) *Anabaenopsis* sp., (D) *Anabaena* sp., and (E) *Oscillatoria* sp. [12, 13].

Table 1 The toxins produced by cyanobacteria and some dinoflagellates and their mechanism of action.

Cyanotoxins	Producers	Chemical classification	Mechanism of action	References
Hepatotoxins				
Microcystins	*Anabaena*, *Planktothrix*, *Nostoc*, *Anabaenopsis, Fischerella, Hapalosiphon, Limnothrix, Lyngbya, Microcystis, Rivularia, Synechocystis* and *Synechococcus*	Cyclic heptapeptides	Protein phosphatases type 1 and 2A inhibited	[20, 21]
Nodularins	*Nodularia*	Cyclic pentapeptídes	Protein phosphatases type 1 and 2A inhibited	[20, 21]
Cylindrospermopsins	*Cylindrospermopsis raciborskii*, *Aphanizomenon ovalisporum* and *Aphanizomenon flos-aquae*	Guanidine alkaloids	Glutathione and protein synthesis as well as cytochrome P450	[22]
Neurotoxins				
Anatoxin-a	*Anabaena, Aphanizomenon* and *Planktothrix*	Alkaloid	Irreversibly bind to the nicotinic receiver S of acetylcholine	[23, 24]
Anatoxin-a(s)	*Anabaena*	Organophosphate	Acetylcholinesterase is inhibited	[25, 26]
Saxitoxins	*Alexandrium, Pyrodinium, Gymnodinium, Anabaena circinalis, Aphanizomenon* sp., *Aphanizomenon gracile, Cylindrospermopsis raciborskii* and *Lyngbya wollei*	Carbamate alkaloids	Sodium channels in nerve axons are blocked	[20, 27]

Antillatoxin	*Lyngbya*	Cyclic depsipeptide	Neuronal coordination is blocked due to binding to the voltage-gated Na^+ channels	[28, 29]
β-*N*-methylamino-L-alanine (BMAA)	*Anabaena, Microcystis, Nostoc* and *Planktothrix*	Peptides	Motor system disorder, glutamate agonist, intracellular concentration of calcium is increased in neurons and activate neuronal activity causing hyperexcitation	[30]
Kalkitoxin	*Lyngbya*	Lipopeptide	Voltage-gated sodium channels are blocked	[31]
Homoanatoxin-a	*Anabaena, Oscillatoria (Planktothrix), Phormidium* and *Raphidiopsis*	Alkaloids	Neuromuscular transmission blocked	[32]
Cyanopeptolin	*Microcystis* and *Planktothrix*	Peptides	Transcriptional changes of genes related to DNA damage and repair	[33]
Dermatotoxins				
Lyngbyatoxin-a	*Lyngbya*	Alkaloid	Potent tumor promoters	[11, 34]
Aplysiatoxin	*Lyngbya, Schizothrix, Planktothrix (Oscillatoria)* and *Trichodesmium*	Alkaloids	Potent tumor promoters	[34]
Lipopolysaccharides (LPS)	Cyanobacteria	Lipopolysaccharides	Inflammatory agents, gastrointestinal irritants	[34, 35]

2.1 Neurotoxins

Neurotoxins are organic molecules that affect the nervous system of vertebrates and invertebrates. Neurotoxins usually have acute effects on vertebrates, with rapid paralysis of the peripheral skeletal and respiratory muscles. Other symptoms include loss of coordination, twitching, irregular gill movement, tremors, altered swimming, and convulsions before death due to respiratory arrest [7, 11].

2.1.1 Anatoxins

Anatoxin-a (Figure 2a) is an alkaloid cyanotoxin that is neurotoxic to mammals and birds [3]. It is produced by *Aphanizomenon* spp. (*Dolichospermum* spp.), *Anabaena, Phormidium*, and *Oscillatoria* [36]. They inhibit transmissions at the neuromuscular junction by mimicking the neurotransmitter acetylcholine (blocks post-synaptic depolarization). They are chemically unstable and degrade in water by photolysis. Therefore, they accumulate to a lesser extent in the tissues of aquatic organisms [11]. Anatoxin-a(s) (Figure 2b) is an N-hydroxyguanidine methyl phosphate ester and is the only known natural organophosphate. It blocks acetylcholinesterase and has been isolated from *Anabaena flos-aquae* in North America, *Anabaena lemmermannii* in Denmark, and *Anabaena crassa* in South America [37]. It is a strong presynaptic and postsynaptic depolarizing agent competing with acetylcholine for nicotinic receptors in the central nervous system (CNS) [38].

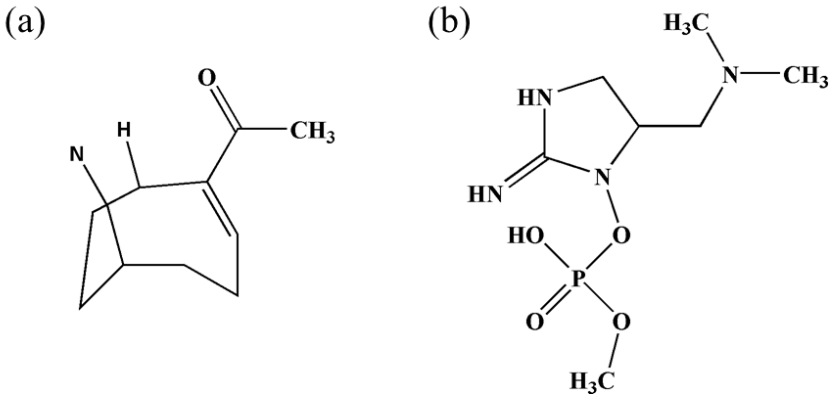

Figure 2 The chemical structures of (a) Anatoxin-a and (b) Anatoxin-a(s).

2.1.2 Saxitoxins

Saxitoxins are heterocyclic guanidines produced by freshwater cyanobacteria and are species-specific. Some examples of saxitoxin-producing cyanobacteria (Figure 3) include *Geitlerinema amphibium*, *Lyngbya wollei, Cylindrospermopsis raciborskii*, *Phormidium uncinatum, Geitlerinema lemmermannii*, and *Cylindrospermum stagnale* [39, 40]. The production and distribution of saxitoxins in *Anabaena* and *Cylindrospermopsis* is associated with environmental stress, especially ionic stress, including those related to pH and Na^+ concentration. When the concentration of Na^+ increases in the medium, the concentration of saxitoxins decreases in *Anabaena circinalis* and increases in *C. raciborskii*, but the ratio of the intracellular and extracellular content remains similar [41]. *Anabaena circinalis* can reduce the production of saxitoxins when the pH increases up

to 9. The complete sequence of the saxitoxin produced by *C. raciborskii* T3 strain encodes 26 genes (sxtA-sxtZ) [42].

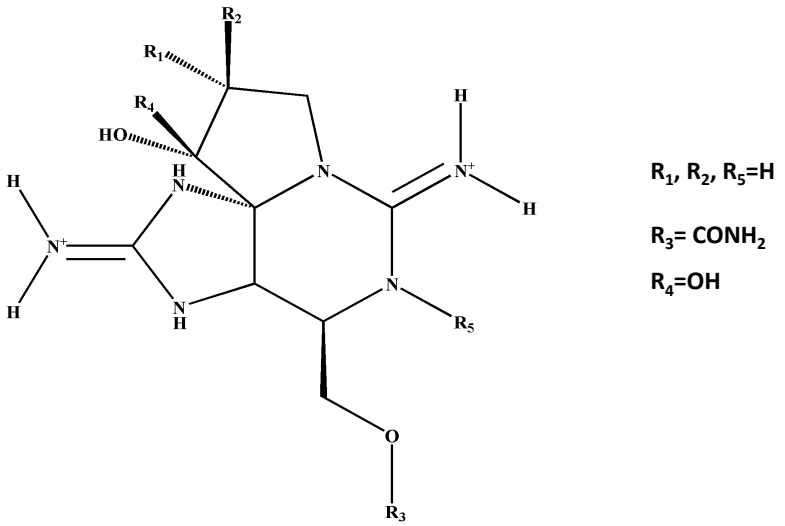

Figure 3 The chemical structure of Saxitoxin.

2.1.3 β-*N*-Methylamino-L-Alanine (BMAA)

BMAA is a non-protein amino acid with a molecular weight of 118 Da (Figure 4). It can be produced by all known groups of cyanobacterial blooms and also by diatoms and dinoflagellates [43]. BMAA exists freely in the environment and tissues but is mostly associated with proteins and can bioaccumulate and biomagnify along the food chain. It is found in *Cycas* seeds and produced by *Nostoc* blooms that have a symbiotic association with the cycad roots (in the Western Pacific) and is transported to the plant [44].

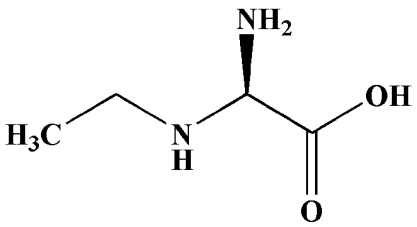

Figure 4 The chemical structure of β-*N*-methylamino-l-alanine.

2.2 Hepatotoxins

Hepatotoxins are produced by many cyanobacterial species and cause the death of fish, birds, wild animals, livestock, and humans around the world [45]. Eukaryotic protein phosphatase type 1 and type 2A are altered by the cyclic heptapeptides or microcystins that cause excessive phosphorylation of cytoskeletal elements resulting in liver failure. They bind to the anion transport system in the hepatocyte cell membranes. [7, 11].

2.2.1 Microcystins

Microcystins (Figure 5) are cyclic heptapeptides with many amino acids and can inhibit protein phosphatases [10]. Microcystins are the largest group of cyanotoxins, with more than 70 structural variants [46]. Microcystin is the only cyanotoxin for which the biosynthetic pathway and the gene cluster have been identified [47]. Their concentrations differ between cyanobacterial blooms and also within a single bloom. Intracellular microcystin content can differ from 10 to 420 femtogram/cell (fg/cell) in *Planktothrix rubescens* and from 100 to 4,000 fg/cell in *Microcystis aeruginosa* [14, 48]. The symptoms of fish poisoning include flared gills because of difficulty in breathing and weakness or the inability to swim. Channel catfish, *Ictalurus punctatus*, can be affected by ~50 to 75 ng microcystin/L [49]. Affected fish may die within 24 h of exposure. Microcystins are produced by *Microcystis*, *Planktothrix*, *Oscillatoria, Dolichospermum* [50], and *Merismopedia* sp. (based on their 2-D sheet morphology) [51]. *Dolichospermum flos-aquae*e and *Dolichospermum lemmermanni* are found in lakes of Norway, Finland, Canada, and also the Baltic Sea [52-54]. A high concentration of microcystins (103 mg/L) caused the death of zebras, blue wildebeest, and rhinos in South Africa [55].

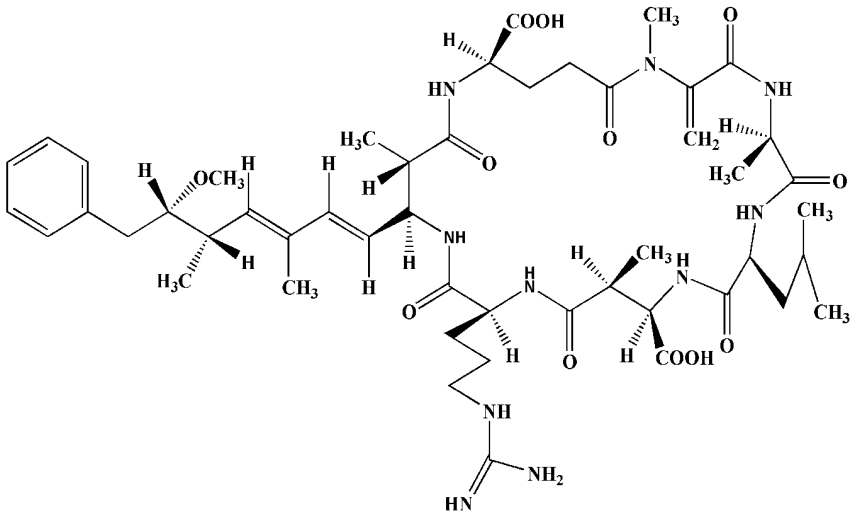

Figure 5 The chemical structure of microcystin.

2.2.2 Nodularins (NOD)

Nodularins are cyclic pentapeptides (Figure 6) structurally similar to microcystins. Nodularins are produced by *Merismopedia minutissima* (based on their 2-D sheet morphology) [51] and *Nodularia spumigena* found in brackish water [56]. *Nodularia* does not form dense colonies and blooms during late summer under nitrogen-deficient conditions. Low or sufficient concentrations of N/P and high temperatures favor their growth [57]. Toxic strains of *Nodularia* are found in Australia, New Zealand, Nevada, and the Baltic Sea [4]. The highest concentrations of NOD have been reported in organisms from the Baltic Sea, for example, 2.5 μg/g in mussels and 0.91 μg/g DW in fish muscle. Nodularins are produced nonribosomally by multienzyme complexes encoded by the *ndaS* gene cluster [58] in *Nodularia spumigena* NSOR10.

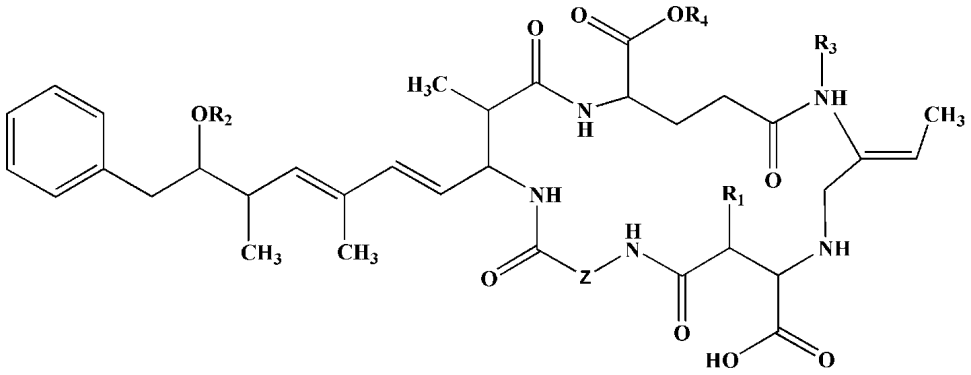

Figure 6 The chemical structure of nodularin.

2.2.3 Cylindrospermopsin (CYN)

Cylindrospermopsin (Figure 7) is a guanidine alkaloid synthesized by *Cylindrospermopsis raciborskii* and several other cyanobacteria. It affects several organs and tissues, inhibiting protein synthesis in plants and animals [20]. *Cylindrospermopsis raciborskii* is a harmful species that caused a waterborne, hepatitis-like illness in humans from Palm Island, Australia, in 1979 [59]. Cylindrospermopsin is also produced by *Anabaena lapponica*, *Aphanizomenon* (*Chrisosporum*) *ovalisporum* [60]*, Raphidiopsis curvata* [29], and *Aphanizomenon flos-aquae* [61]. It shows hepatotoxic, nephrotoxic, and cytotoxic effects and acts as a carcinogen. It inhibits glutathione, cytochrome P450, and protein synthesis [62] (Figure 8). The highest concentration of cylindrospermopsin (173 μg/L) was found in an arid lake in Saudi Arabia [63]. Photodegradation occurs in the natural environment and depends on the water depth. *Aeromonas* sp. can remove cylindrospermopsin and the efficiency of removal depends on the pH and temperature [64]. Generally, cylindrospermopsin is present in small amounts in drinking water, but it was found in tap water samples (0.69 - 2.2 μg/L) from the Kinmen Island [65]. Cylindrospermopsin is hydrophilic, and its intestinal absorption and uptake into hepatocytes may be mediated by an active transport system such as the bile acid transport system, e.g., cholate and taurocholate.

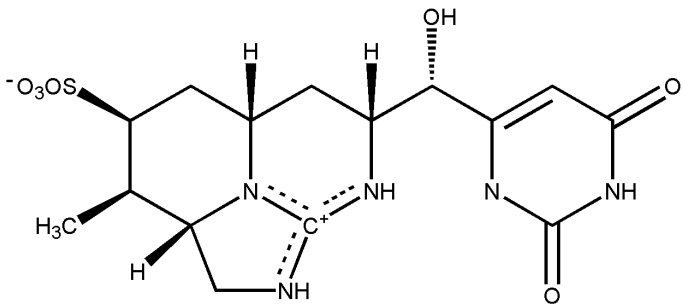

Figure 7 The chemical structure of Cylindrospermopsin.

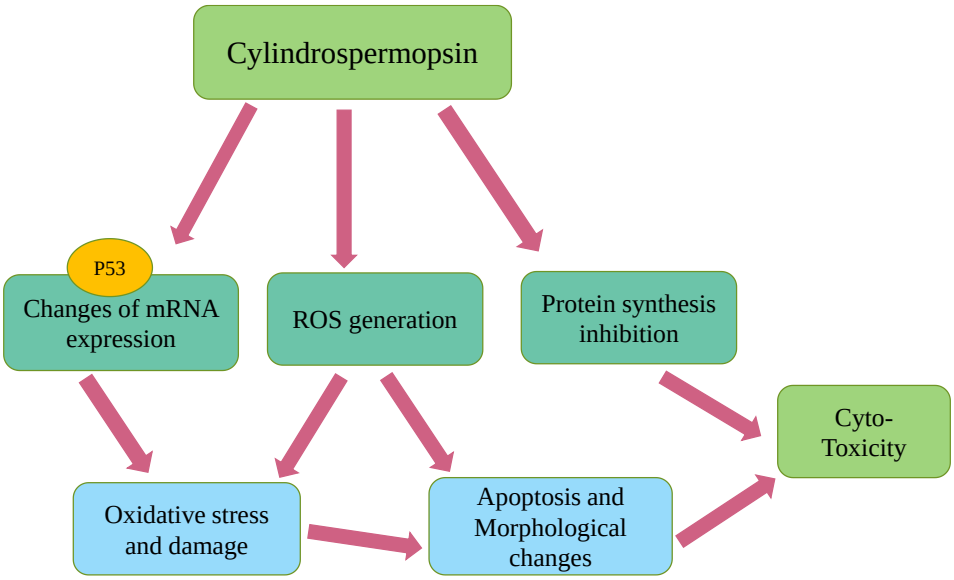

Figure 8 The pathways illustrate the mechanism of action of cylindrospermopsin (modified from [66])**.**

2.3 Dermatotoxin

2.3.1 Lipopolysaccharides (LPS)

Lipopolysaccharides (Figure 9) are present in the outer membrane of Gram-negative bacteria, including cyanobacteria [3, 67]. They cause blisters, gastrointestinal disorders, and human skin irritation. Other skin irritants and inflammatory cyanotoxins produced by marine cyanobacteria are jamaicamides, aplysiatoxins, and lyngbyatoxins [7]. *Anacystis nidulans*, *Microcystis*, *Anabaena*, *Spirulina*, and *Oscillatoria,* produce LPS toxins [68].

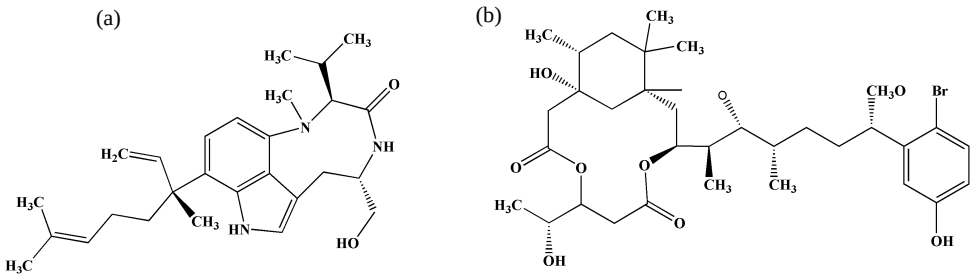

Figure 9 The chemical structures of (a) lyngbyatoxins and (b) aplysiatoxins.

3. Factors Affecting Cyanobacterial Blooms

3.1 Eutrophication

Nutrient pollution, such as that due to nitrogen (N) and phosphorus (P) (Figure 10), has increased in aquatic ecosystems due to various anthropogenic activities and gained more attention than other environmental drivers. Nutrient loading has increased due to wastewater and runoff from impervious surfaces. Atmospheric pollution has increased due to the increase in the rates of fossil fuel combustion in urbanized areas [69]. Eutrophication is responsible for the

excessive growth of cyanobacteria or cyanobacterial blooms. Other harmful algal blooms (HABs) have also increased due to the increase in the human population [1]. When the nutrient content of freshwater bodies increases excessively (predominantly P), the phytoplankton community is dominated by cyanobacteria [70]. Experimental models speculate that in hot environmental conditions and summer, phytoplankton communities are dominated by cyanobacteria for P concentrations of ~ 100 - 1,000 µg L^{-1} [71].

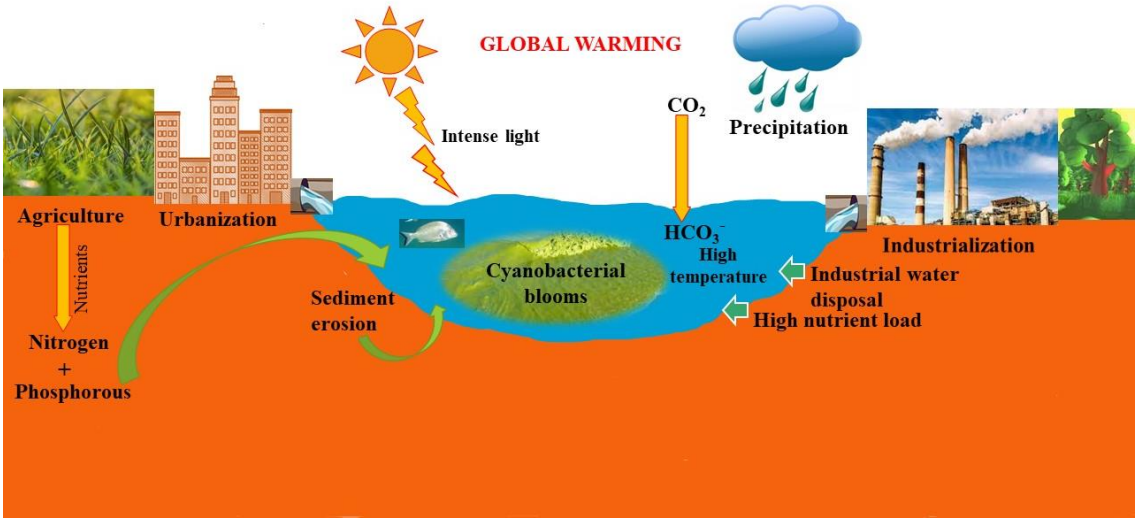

Figure 10 Several factors affect cyanobacterial blooms, such as eutrophication, global warming, and increasing CO_2 concentrations. Global warming affects cyanobacterial blooms by increasing temperatures and light intensity. Cyanobacteria have evolved advanced CO_2-concentrating mechanisms such as the uptake systems of atmospheric CO_2 and bicarbonate ions. Nutrient pollution, such as those associated with nitrogen and phosphorus, has increased in aquatic ecosystems due to urban and agricultural discharges and is responsible for eutrophication which causes cyanobacterial blooms (Illustration by S. Mishra).

The potential of cyanobacteria to uptake organic P with phosphatases and to retain abundant P vary across species. Fifty cyanobacterial strains in about 10 genera show remarkable differences in their ability to uptake P from different organic molecules [72]. Some Rivulariaceae and non-Rivulariaceae were tested to determine the production of nutrient P from most organic molecules. Rivulariaceae such as *Calothrix, Dichothrix*, and *Gloeotrichia* yielded a higher level of P than non-Rivulariaceae such as *Anabaena, Fischerella, Lyngbya*, and *Tolypothrix*. Among the tested cyanobacterial genera, *Gloeotrichia* notably expressed high extracellular phosphomonoesterase (PMEase) activity [72]. Similarly, variability in the capacity to store abundant P might exist in cyanobacteria. It could be more beneficial to some taxa relative to others during P deficiency. For example, *Anacystis* can take up more P than *Anabaena*, *Plectonema*, and *Synechococcus* [73].

Several cyanobacterial genera are responsible for forming blooms, where some species may be controlled by the availability of P and N [70, 74]. Cyanobacteria-rich water bodies that play a role in bloom formation are known as cyanobacterial pools. Several studies have investigated cyanobacterial blooms to determine the level of P and N in cyanobacterial pools. Most

cyanobacterial pools that consist of soluble N and P are composed of organic compounds [75]. The soluble or dissolved organic N and P are used by several cyanobacteria [74].

Inorganic nutrient pools are insufficient as a source of organic nutrients to account for the long duration of dense cyanobacterial blooms [1]. Researchers must examine the effects of all nutritive species and micronutrients such as Fe to comprehensively understand the factors that influence the density of cyanobacterial blooms. The effect of Fe is also found in diazotrophs as they require high levels of Fe for the enzyme nitrogenase, and thus, many studies have determined the effect of Fe on diazotrophs [76]. The recent development of molecular examinations for cyanobacteria has helped to understand how harmful cyanobacteria respond to various nutrients at the cellular level.

3.2 Global Warming

Global warming affects cyanobacteria in different ways by increasing the temperature and light intensity (Figure 10). Cyanobacteria grow rapidly in warmer water and a brighter environment [77]. *Cylindrospermopsis raciborskii* can grow profusely in freshwater under different environmental conditions and become toxic by bloom formation [78]. This species grows optimally at 30 °C [78]. *Trichodesmium* is a nitrogen-fixing marine cyanobacterium adapted to live under conditions of low nutrient, bright light, and clear surface water found in tropical and subtropical oceans [79]. Many cyanobacterial species grow better in warm water. *Trichodesmium erythraeum* bloomed in the Canary Islands Archipelago in August 2004, the hottest period (27.5 °C) recorded since 1912 [80]. A *T. erythraeum* bloom had not previously been recorded anywhere along the boundary of the African upwelling zone. This bloom was associated with unusual dust storms and warm weather in the area [80]. *Trichodesmium* bloom may also favor increased vertical stratification that is enhanced by the warming of sea surface waters. Cyanobacteria are found predominantly in the warmer months in subtropical estuaries (Pensacola Bay, FL) [81].

An increase in the frequency of blooming of a marine benthic *Lyngbya* sp. was recorded in the nearshore environments in the past decade [82, 83]. The active growth of *Lyngbya majuscula* resulted in bloom formation, which was recorded in Moreton Bay, Australia, for several years. Several environmental parameters were evaluated before and during the bloom to determine the factors responsible for bloom dynamics [84]. The authors were monitoring a pulse of rainfall before the *Lyngbya* bloom, and periods of the high incident light, water temperatures above 24 °C, and cool weather were associated with the onset of the bloom. The cyanobacterium *Phormidium corallyticum* shows the highest photosynthetic activity in oxygenic environments at water temperatures of 30 - 37 °C.

Common corals are attacked by the black band disease that is caused by cyanobacteria, of which, *Phormidium corallyticum* is the prime constituent of the microbial consortium [85]. Many cyanobacterial species influence not only their growth rate but also their toxin production in response to light and temperature [86]. Toxin production in *Microcystis aeruginosa* increased as a response to irradiation under low-light conditions [87]. The microcystin composition of *Planktothrix agardhii* shifted with an increase in the amount of a toxic variant associated with high light intensity [88]. However, cyanobacteria did not grow densely under warm experimental conditions [89].

3.3 Increasing CO_2 Concentrations

The partial pressure of CO_2 in the atmosphere is correlated with the concentration of dissolved CO_2 in water. However, cyanobacterial blooms can endure rising CO_2 concentrations due to their photosynthetic capacity [90]. Cyanobacteria have evolved advanced CO_2-concentrating mechanisms such as uptake systems of CO_2 and bicarbonate [91, 92]. Eukaryotic phytoplankton (green algae) are superior competitors at high concentrations of dissolved CO_2, while prokaryotic phytoplankton (cyanobacteria) are better competitors at low concentrations of dissolved CO_2 [93].

Various inorganic carbon uptake systems are regulated in cyanobacteria by many pathways, causing significant differences in CO_2 responses across taxa [92, 94]. *Microcystis* strains with high-affinity bicarbonate uptake systems are favored at low concentrations of dissolved CO_2, as confirmed by selection experiments and lake examination [92, 95]. Additionally, at high concentrations of dissolved CO_2, the *Microcystis* strains, with a higher affinity to uptake bicarbonate than eukaryotic phytoplankton, are favored [96]. This study argues that the genetic diversity and physiological flexibility of cyanobacterial CO_2-concentrating mechanisms enable quick acclimatization of bloom-forming cyanobacteria to high CO_2 concentrations. Sharp CO_2 gradients at the air-water interface increase the flow of CO_2 into the surface layer, which can be prevented by surface-dwelling blooms [97]. Laboratory experiments and mathematical models speculate that cyanobacterial blooms are probably accelerated in eutrophic and hypertrophic waters in response to increasing atmospheric CO_2 concentrations [90, 96].

4. Effects of Cyanotoxins on Humans and Animals

The cytotoxic effects related to cyanotoxin ingestion, dermal contact, or intraperitoneal injection have been reported in several studies [98-99]. Respiratory symptoms are the most common complaints, and specific respiratory reactions associated with cyanobacterial blooms include sore throat, hay fever, and cough [98]. Inflammatory responses may occur in humans after inhaling cyanobacterial compounds in the air [99]. Various types of cyanotoxins and many analogs are produced by cyanobacterial blooms that vary in toxicological potential and other properties. Also, animal and *in vitro* studies have reported that crude cell extracts are more potent than dose-equivalent quantities of cyanotoxins [100].

4.1 Cylindrospermopsin

Cylindrospermopsin affects the liver and kidneys. Acute hepatic damage is confined to the centrilobular areas causing hepatocyte vacuolization and enhanced pigmentation of the nucleus and the cytoplasm. Renal toxicity is associated with necrosis, and the lumen of proximal tubules widens and changes in the glomerulus. Cytotoxic effects are related to oxidative stress due to an increase in H_2O_2 in a concentration-dependent manner, a reduction in the activity of SOD and CAT, an increase in glutathione peroxidase and apoptosis, and a decrease in the potential to fight pathogenic microorganisms [101, 102]. Human peripheral blood neutrophils react to cylindrospermopsin (0.01 - 1 μg/mL), which reduces the production of reactive oxygen species (ROS) [103]. Apoptosis occurs in the human umbilical vein endothelial cell line (HUVEC) cells, causing morphological changes, including nucleolar segregation with altered nuclei, deterioration of the Golgi apparatus, and increase in granules. In primary rat hepatocytes, cylindrospermopsin

induces transcription of the antioxidant response element (ARE)-binding factor, Nrf2. When RBCs (red blood cells) were exposed to cylindrospermopsin for 21 days, they showed abnormal spikes and very high cholesterol levels in the RBC membrane due to the inhibition of plasma lecithin cholesterol acyl transferase [104]. Chromosome alterations were not observed in Chinese hamster ovary (CHO)-K1 cells exposed to CYN with or without metabolic activation [105]. A high cylindrospermopsin concentration resulting from a cyanobacterial bloom caused the death of cattle in north Queensland [106]. CYN may impede the functions of fish phagocytic cells and affect their immunity [107].

4.2 Nodularins

Nodularins inhibit protein phosphatases, mainly PP2A (IC50 = 0.17 nM in the human red blood cell) [108]. NOD induces inflammation, endoplasmic reticulum (ER) stress, and associated unfolded protein response (UPR) in liver cells by acting through tumor necrosis factor α (TNF-α) [109]. NOD impedes nuclear excision repair (NER) by deactivating the excision repair cross complementation group 1-XPF and activating oxidative DNA damage in the human hepatoblastoma cell line HepG2 and the Chinese hamster ovary (CHO) cells [110]. NODs promote tumors, and in the two-stage carcinogenesis model in rats, NOD (25 μg/kg bw i.p.) activates the formation of placental glutathione S-transferase (GST-P) liver foci in initiated animals. NOD alone can cause hepatocyte growth until week 18 and also induce apoptosis and hyperphosphorylation of signaling proteins in cultured rat hepatocytes [111]. In the flatfish, *Platichthys flesus*, NODs cause oxidative stress resulting in the reduction of GST and CAT activity leading to an increase in the vulnerability of the cells to ROS [112].

4.3 Saxitoxins

Saxitoxins block voltage-gated Na^+ neuron channels and arrest the transmission of action potentials resulting in rapid paralysis [113]. They accumulate in shellfish, and the related human illness is known as paralytic shellfish poisoning. Anatoxin-a can affect blood pressure, heart rate, and gas exchange, causing hypoxia, respiratory arrest, and severe acidosis, resulting in the death of the animals [114]. Antillatoxin is a novel ichthyotoxic (LC_{50} = 0.1 μM) substance isolated from *Lyngbya majuscula* [115]. Kalkitoxin (Figure 11) is toxic to the goldfish (*Carassius auratus*) and the brine shrimp (*Artemia salina*) with an LC_{50} of 700 and 170 nM, respectively [116].

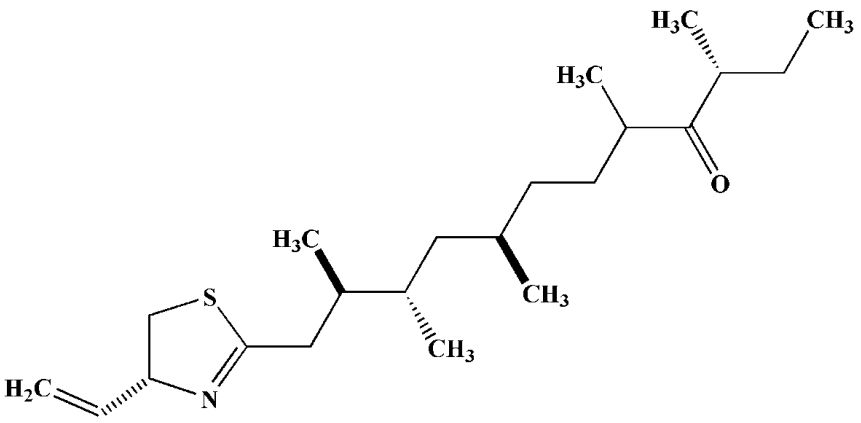

Figure 11 The chemical structure of Kalkitoxin.

4.4 Microcystins

Microcystins (MCs) can cause normocytic anemia and severe liver damage; other mammalian tissues are also affected. Additionally, MCs can have tumor-promoting, pulmonary, neurological, and reproductive effects [117]. Serine/threonine type 1 and 2A protein phosphatases (PP1 and PP2A, respectively) are inhibited by microcystin. Microcystin is not mobilized from the lung to the liver and the respiratory tract, indicating that it cannot easily cross the blood-air barrier in the lungs. Cyanobacterial bloom cells may be deposited in the lower respiratory tract [118]. Two types of human bronchial epithelial (HBE) cells express genes encoding organic anion transport proteins that are responsible for the cellular uptake of MC-LR [119]. At necropsy, severe lesions may be observed in liver tissues. MC-LR causes normocyte anemia and bone marrow injury and also affects the immune system of rabbits [120]. They also cause hepatotoxicity and neurotoxicity, kidney impairment, allergies, eye, ear, and skin irritation, and some gastrointestinal disorders such as nausea/vomiting and diarrhea in humans [19]. The large-scale death of lesser flamingos (*Phoeniconaias minor* Geoffroy) was reported in lake Manyara of Tanzania due to microcystin toxicity [121], where at least 6,000 birds belonging to 47 species, including endangered species such as the marbled teal (*Marmaronetta angustirostris*) and white-headed duck (*Oxyura leucocephala*), died due to the toxic effects of MC-LR at the Doñana National Park, Spain [122].

4.5 Lipopolysaccharides

Lipopolysaccharides (LPSs) cause fever in mammals and are involved in septic shock syndrome and liver injury [123]. They can impair the immune system and also affect the detoxification system of various organisms [124]. The function and effect of BMAA on human health are not well-known, but due to neurotoxic properties, it can cause severe neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). It might be incorporated in proteins, causing protein misfolding and leading to several neurodegenerative diseases [125]. BMAA affects motor neurons *via* many mechanisms; for example, BMAA can act on glutamate NMDA (*N*-methyl d-aspartic acid) and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors or induce oxidative stress and reduce glutathione [30].

5. Effects of Cyanobacterial Blooms on Aquatic Ecosystems

5.1 Effects of Cyanobacterial Blooms on Community Dynamics

Alterations in benthic and planktonic microbial communities are caused by cyanobacterial blooms. The composition of cyanobacterial species changes due to considerable shifts in the cyanosphere community [126]. Significant alterations in the taxonomic composition and gene expression of the cyanosphere community might occur with the different phases of bloom development. Mainly, heterotrophic bacteria related to the biodegradation of complex organic molecules become prominent during the lysis of cyanobacterial blooms [127]. In lake Taihu, microcystin degrading alphaproteobacteria of the family Sphingomonadaceae dominated the cyanosphere during the decomposition of a *Microcystis* bloom [128].

The temperature of the surface blooms in the Baltic Sea was approx. 1.5 °C above that of the ambient water [129]. The surface temperatures within cyanobacterial blooms in lake Ijsselmeer,

Netherlands, were higher than those in the blooms of the surrounding surface waters [130]. Cyanobacteria can increase surface temperatures, which increases their competitive dominance over eukaryotic phytoplankton.

5.2 Other Effects of Cyanobacterial Blooms on the Ecosystem

Cyanobacterial blooms disrupt ecosystems by producing toxins, and several organisms are affected at different trophic levels. Cyanobacterial blooms adversely affect ecosystems by producing large amounts of organic matter, even without producing toxins, following bloom senescence. Huge amounts of decaying biomass are found at the bottom of the water bodies due to bloom die-offs, which cause hypoxic and anoxic conditions. Several benthic dwellers die due to low dissolved oxygen. Hence, the benthic diversity declines, resulting into the loss of primary producers and reduced food web functioning. The effect continues throughout the food web as enough nutrients are not available to the biota at intermediate and upper levels. This results in the loss of biological diversity at all levels, including the reduction in the population size of organisms that serve humans as food sources, food stock, and recreational activities. Habitat loss may also affect ecosystem sustainability leading to the growth of less desirable populations such as toxigenic cyanobacteria due to the absence of competition. Cyanobacterial blooms are generally found in areas with poor water quality and environments impeded by various stressors. The associated effects of the stressors are antagonistic or additive. This causes considerable ecological changes as the ecosystem reaches an ecological threshold beyond which it is unable to revert to its original state [100].

Aquatic organisms may be harmed either through direct ingestion of toxic cyanobacterial cells or through contact with cyanotoxins. Cyanotoxins can affect *Daphnia pulicaria*, reducing its filtration capacity and survival of offspring [131]. Cyanotoxins also affect algae, diatoms, and plants. Fischerellin, produced by *Fischerella muscicola*, inhibits the photosynthesis of other cyanobacteria [132]. Microcystin affects neuromuscular communication and, thus, significantly reduces the beat rates of the thoracic legs, mandibles, foregut, and second antennae in *Daphnia*. It also arrests the peristaltic movements of the midgut. *Daphnia* specimens that are fed microcystin-producing PCC 7806 wild-type cells suffer lethal poisoning. Consumption of microcystin (10.2 ng and 18.3 ng /mg body weight) caused rapid death of *Daphnia galeata* [133]. Low doses of microcystin do not affect *Daphnia magna* but high concentration for a long time inhibits the activity of the enzyme phosphatase [134]. Microcystins inhibit photosynthesis and growth and also cause the cells of *Nostoc muscorum* and *Anabaena* to break [135]. *Anabaena lemmermannii*, *Aphanizomenon flos-aquae*, and *Nodularia spumigena* inhibited the growth of the red alga *Rhodomonas* sp. and the diatom *Thalassiosira weissflogii in vitro* [136]. Microcystin (1.0 μgL^{-1}) decreased the growth of *Ceratophyllum demersum* [137]. Microcystin can accumulate in tissues of *Lymnaea stagnalis* and reduce egg production [138]. *Dreissenia polymorpha* mussels fed on *Microcystis aeruginosa* CCAP 1450/10 showed a reduction in food intake, filtration, absorption, and fecal loss, and the net energy balance was impaired [139].

Saxitoxins produced by *Aphanizomenon issastchenkoi* decreased the somatic growth of *Daphnia magna*; also, reproduction rates of *Daphnia pulex* and *Moina micrura* were reduced by saxitoxins produced by *C. raciborskii* [140, 141]. Cyanobacterial blooms can also harm fish by damaging the gills, digestive tract, and liver, causing death. The intake of microcystin increases

after gill damage and leads to liver necrosis. Cyanobacterial blooms cause damage to the liver, heart, kidney, skin, gills, and spleen [34]. The effects of microcystins on various species of fish are summarized in Table 2. Generally, juvenile and sub-adult fish are more sensitive to toxic compounds than their adult counterparts. This may be due to the presence of a thin epithelial layer, relatively large body surface area, and high metabolic rate [142].

Cyanobacterial blooms affect the larval development in the carp *Cyprinus carpio*. *Microcystis* sp., *Aphanizomenon flos-aquae*, and *Planktothrix agardhii* showed embryotoxic effects such as significant fish mortality, delayed hatching, lower number of hatched embryos, the suppression of embryonic development, problems in filling the air bladder, and significant inhibition of glutathione S-transferase (GST). Survival rates decreased to 40% and 20% when the embryos of *Danio rerio* were given 50 or 5 μg/L MC-LR and MC-RR, respectively. Anatoxin-a caused fast opercular movement and abnormal swimming in *Cyprinus carpio*. Exposure to 400 μg/L of anatoxin-a changed the heart rate at several developmental phases of *Danio rerio* [143]. When *Danio rerio* embryos were given 500 μg/L saxitoxin, 34% of the embryos showed abnormal development; mainly, abnormalities in the lateral and ventral body curvature, edema, and mortality occurred during larval development after 21 days. Saxitoxins of *Cylindrospermosis raciborskii* changed the swimming behavior of *Danio rerio* [144]. Dissolved saxitoxins also reduced the spontaneous swimming behavior and touch response in larval herring (*Clupea harengus pallasi*) [145].

Table 2 The effects of microcystins in fishes.

Species	Microcystin concentration	Effects	References
Misguruns mizolepis	0-500 μg MC-LR/L	Pericardial edema and tubular heart, bradycardia, homeostasis, poor yolk resumption, small head, curved body and tail, abnormal hatching	[142]
Leuciscus cephalus	0.5, 5, 50 μg MC-LR	Survival rate reduced	[146]
Danio rerio	0.5, 5, 50 μg MC-LR	Survival rate and growth reduced	[143]
Oryzias latipes	1-10 μg/mL MC-LR	Death of embryos, hepatic hemorrhage and necrosis at late developmental phases	[147]
Oncorhynchus mykiss	0.5, 5, 50 μg MC-YR	Hatching was stimulated	[143]
Coregonus lavaretus	0.5, 5 mg MC-LR	Hatching delayed	[148]
Cyprinus carpio L.	9.6 mg MC-YR	Larval death, prolonged hatching	[149]

6. Management Strategies for Cyanobacterial Blooms

Several management strategies, such as nutrient load reduction, hydrodynamic changes, and chemical and biological control have been developed to stop cyanobacterial blooms.

6.1 Nutrient Load Reduction

Nutrient load reduction can effectively improve water quality. The nutrient load can often be manipulated and, therefore, should be a central part of the strategy to mitigate cyanobacterial blooms. Nutrient load reduction requires national and international efforts in eutrophic, cyano-bloom susceptible lakes, rivers, estuaries, and coastal waters through a broad range of diffuse and point sources. In the 1970s and 1980s, the use of P in detergents was banned, and strict regulations were implemented on the use of N and P fertilizers to reduce nutrient contamination. Despite this step, it can take many years or even decades to successfully reduce external nutrients [150, 151] and recycle internal nutrients, especially P, from lake sediments [152]. Additionally, delays in recovery might occur if the initial period of eutrophication has progressed in a lake ecosystem that is more resistant to change and is in a potentially stable state [153].

In many lakes, besides P binding soils, shifting of the lake sediment by sediment capping has been implemented to reduce internal P loading and promote lake recovery [154, 155]. Additionally, sediments from shallow waters can be more readily reabsorbed by aerial and benthic organisms. For example, fish can reintroduce nutrients into the water column. Accordingly, these approaches for controlling blooms can be used simultaneously with external nutrient depletion for successful and extensive mitigation of blooms [156].

6.2 Hydrodynamics

To suppress cyanobacterial blooms, the artificial mixing of lakes may be an expensive but efficient process [97]. In this process, the cyanobacterial bloom is prevented by vertical mixing that overtakes the flotation velocity. Thus, the cyanobacteria are replaced by diatoms and green algae [97, 157]. Elevated water flow or hydrodynamics can reduce cyanobacterial blooms and provide an effective mitigation strategy for stagnant rivers and reservoirs [158].

6.3 Chemical Control

Although chemical treatment can rapidly eliminate cyanobacterial blooms, it is a short-term solution. The chemically controlled mechanism of cyanobacterial blooms has not been approved because the chemicals persist in the environment. Chemicals such as copper sulfate, diuron, and many other algicides have toxic effects on other aquatic organisms [159]. Moreover, cell lysis and the release of cyanotoxins are also caused by the chemical treatment, which deteriorates water quality. Cyanobacteria are more sensitive to hydrogen peroxide than eukaryotic phytoplankton, and thus, cyanobacterial blooms are effectively eradicated using low concentrations of hydrogen peroxide [160, 161]. A major benefit of this method is that the added hydrogen peroxide decays into water and oxygen within a few days and does not leave any chemical traces in the environment [160].

6.4 Biological Control

Cyanobacterial blooms can be controlled biologically, but this management strategy is not simple. Cyanobacterial blooms might be regulated effectively by the application of viruses, pathogenic bacteria, and fungi [162]. However, the occurrence of many resistant cyanobacterial strains renders these host-specific microbial antagonists ineffective [161, 163]. Viral or fungal

contaminations can cause rapid destruction of cyanobacterial biomass but rarely elicit a long-term reduction in cyanobacterial blooms [163, 164]. Mollusks, such as the zebra mussel *Dreissena polymorpha*, filter water abundantly and eliminate phytoplankton and other suspended particles. The effect of *Dreissena polymorpha* on cyanobacterial blooms is under investigation. Dreissenid mussels from European lakes can significantly reduce cyanobacterial blooms since they filter many species of cyanobacteria, regardless of their toxicity [165].

In the Great Lakes of North America, dreissenid mussels can filter most single cells and small colonies. These lakes favor large and buoyant colonial cyanobacteria [166]. Zebra mussel invasions in the 1980s and 1990s occurred simultaneously with *Microcystis* blooms in Lake Erie and Lake Huron [167]. The zebra mussels of Europe and North America may vary in their genetic traits, adaptation history, and nutrient status [168]; these differences may have different effects and require further investigation. In many shallow lakes, the entire food web is disrupted by the elimination of planktivorous and benthivorous organisms and the addition of piscivorous fish[7, 142, 146]. Phytoplankton biomass is under the control of bio-direction. Bio-direction or biocontrol helps in suppressing fish-induced sediment resorption and increases the abundance of large zooplankton. Submerged macrophytes increase water transparency. The accessible nutrients are captured by the submerged macrophytes; thus, suppressing further sediment resorption and making the water clearer. Preliminary results are promising in waters with elevated internal nutrient load and continuous external nutrient inputs [169]. Therefore, this strategy might be worthwhile in the long term, provided the external nutrient load is effectively reduced [169, 170].

7. Conclusion

Cyanobacteria can rapidly colonize aquatic ecosystems. The continued eutrophication, global warming, and increasing atmospheric CO_2 concentrations are responsible for an increase in the incidence, intensity, and duration of harmful cyanobacterial blooms. Cyanobacterial blooms produce various secondary metabolites, and most of these are cyanotoxins which are harmful to plants, invertebrates, and vertebrates, including humans, at naturally occurring concentrations. These blooms adversely affect potable and irrigation water supplies, other recreational sources, and fisheries [171]. Bloom-forming cyanobacteria and their uncontrolled growth are the cause of many complications and require large-scale efforts to regulate bloom formation. Along with nutrient depletion, authorities tackling cyanobacterial blooms have to consider the physicochemical and hydrological effects of climate change in their management strategies, accounting for regional, climatic, and anthropogenically driven changes. Studies that focus on the effects of cyanobacterial blooms and their toxins on the individual components of ecosystems and their interactions need to be conducted. This could be achieved by performing culture, microcosm, mesocosm, and ecosystem field studies. Removing water from deep within the reservoir could be an effective strategy to minimize the algal concentrations in the water supply during cyanobacterial blooms. Additional observational studies are required to understand the process of excess bloom formation and regulate the species composition and production of cyanotoxins. Suitable management strategies, such as nutrient load reduction, hydrodynamics, biological control, and chemical control strategies, are required for bloom reduction. Some of these strategies were successful in the long term, while others had only short-term effects.

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Author Contributions

S. Mishra and N. Kumari wrote the manuscript. RP Sinha and D-P Häder conceptualized the topic, and edited the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Heisler J, Glibert PM, Burkholder JM, Anderson DM, Cochlan W, Dennison WC, et al. Eutrophication and harmful algal blooms: A scientific consensus. Harmful Algae. 2008; 8: 3-13.
2. Scheffer M, Hosper SH, Meijer ML, Moss B, Jeppesen E. Alternative equilibria in shallow lakes. Trends Ecol Evol. 1993; 8: 275-279.
3. Metcalf J, Codd G. Cyanotoxins. In: Ecology of cyanobacteria II: Their diversity in space and time. Dordrecht: Springer; 2012. pp. 651-675.
4. Merel S, Walker D, Chicana R, Snyder S, Baurès E, Thomas O. State of knowledge and concerns on cyanobacterial blooms and cyanotoxins. Environ Int. 2013; 59: 303-327.
5. Paerl HW, Paul VJ. Climate change: Links to global expansion of harmful cyanobacteria. Water Res. 2012; 46: 1349-1363.
6. Paerl HW, Huisman J. Blooms like it hot. Science. 2008; 320: 57-58.
7. Rastogi RP, Sinha RP, Incharoensakdi A. The cyanotoxin-microcystins: Current overview. Rev Environ Sci Bio/Technol. 2014; 13: 215-249.
8. Neilan BA, Pearson LA, Muenchhoff J, Moffitt MC, Dittmann E. Environmental conditions that influence toxin biosynthesis in cyanobacteria. Environ Microbiol. 2013; 15: 1239-1253.
9. Häder DP, Villafañe VE, Helbling EW. Productivity of aquatic primary producers under global climate change. Photochem Photobiol Sci. 2014; 13: 1370-1392.
10. MacKintosh C, Beattie KA, Klumpp S, Cohen P, Codd GA. Cyanobacterial microcystin-LR is a potent and specific inhibitor of protein phosphatases1 and 2A from both mammals and higher plants. FEBS Lett. 1990; 264: 187-192.
11. Funari E, Testai E. Human health risk assessment related to cyanotoxins exposure. Crit Rev Toxicol. 2008; 38: 97-125.
12. Mishra S, Pandey A, Ahmed H, Kumar D, Singh V, Sinha RP. Mycosporine-like amino acids (MAAs) profile of cyanobacteria from different historical kunds of Varanasi, India. Int J Appl Sci Bio. 2019; 7: 317-326.
13. Mishra S, Pandey A, Sinha RP. Characterization of photoprotective and pharmaceutically important compounds from cyanobacteria and algal assemblages from historical kunds of Varanasi, India. J Chem Pharm Res. 2019; 11: 24-36.

14. Sabart M, Misson B, Descroix A, Duffaud E, Combourieu B, Salencon MJ, et al. The importance of small colonies in sustaining Microcystis population exposed to mixing conditions: An exploration through colony size, genotypic composition and toxic potential. Environ Microbiol Rep. 2013; 5: 747-756.
15. Westrick JA, Szlag D. A cyanotoxin primer for drinking water professionals. J Am Water Work. Assoc. 2018; 110: E1-6.
16. Chapra SC, Boehlert B, Fant C, Bierman Jr VJ, Henderson J, Mills D, et al. Climate change impacts on harmful algal blooms in US freshwaters: A screening-level assessment. Environ Sci Technol. 2017; 51: 8933-8943.
17. Berry JP, Gantar M, Perez MH, Berry G, Noriega FG. Cyanobacterial toxins as allelochemicals with potential applications as algaecides, herbicides and insecticides. Mar Drugs. 2008; 6: 117-146.
18. Sunda WG, Graneli E, Gobler CJ. Positive feedback and the development and persistence of ecosystem disruptive algal blooms. J Phycol. 2006; 42: 963-974.
19. Codd GA, Morrison LF, Metcalf JS. Cyanobacterial toxins: Risk management for health protection. Toxicol Appl Pharmacol. 2005; 203: 264-272.
20. Pearson L, Mihali T, Moffitt M, Kellmann R, Neilan B. On the chemistry, toxicology and genetics of the cyanobacterial toxins, microcystin, nodularin, saxitoxin and cylindrospermopsin. Mar Drugs. 2010; 8: 1650-1680.
21. Mulvena V, Dale K, Priestly B, Mueller U, Humpage A, Shaw G, et al. Health risk assessment for cyanobacterial toxins in seafood. Int J Environ Res Public Health. 2012; 9: 807-820.
22. Kehr JC, Picchi DG, Dittmann E. Natural product biosynthesis in cyanobacteria: A treasure trove of unique enzymes. Beilstein J Org Chem. 2011; 7: 1622-1635.
23. Ferrão Filho AD. Bioacumulação de cianotoxinas e seus efeitos em organismos aquáticos. Oecol Bras. 2009; 13: 272-312.
24. Falconer IR, Humpage AR. Health risk assessment of cyanobacterial (blue-green algal) toxins in drinking water. Int J Environ Res Public Health. 2005; 2: 43-50.
25. Rodríguez V, Moura S, Pinto E, Pereira CM, Braga RC. Aspectos toxicológicos e químicos da anatoxina-a e seus análogos. Quím Nova. 2006; 29: 1365-1371.
26. Falconer IR. Health effects associated with controlled exposures to cyanobacterial toxins. In: Cyanobacterial harmful algal blooms: State of the science and research needs. New York, USA: Springer; 2008. pp. 607-612.
27. Bláha L, Pavel B, Blahoskav M. Toxins produced in cyanobacterial water blooms—toxicity and risks. Interdiscip Toxicol. 2009; 2: 36-41.
28. Berman FW, Gerwick WH, Murray TF. Antillatoxin and kalkitoxin, ichthyotoxins from the tropical cyanobacterium Lyngbya majuscula, induce distinct temporal patterns of NMDA receptor-mediated neurotoxicity. Toxicon. 1999; 37: 1645-1648.
29. Li R, Carmichael WW, Brittain S, Eaglesham GK, Shaw GR, Liu Y, et al. First report of the cyanotoxins cylindrospermopsin and deoxycylindrospermopsin from Raphidiopsis curvata Cyanobacteria. J Phycol. 2001; 37: 1121-1126.
30. Lobner D, Piana PM, Salous AK, Peoples RW. β-N-methylamino-L-alanine enhances neurotoxicity through multiple mechanisms. Neurobiol Dis. 2007; 25: 360-366.

31. LePage KT, Goeger D, Yokokawa F, Asano T, Shioiri T, Gerwick WH, et al. The neurotoxic lipopeptide kalkitoxin interacts with voltage-sensitive sodium channels in cerebellar granule neurons. Toxicol Lett. 2005; 158: 133-139.
32. Lilleheil G, Andersen RA, Skulberg OM, Alexander J. Effects of a homoanatoxin-a-containing extract from Oscillatoria formosa (cyanophyceae/cyanobacteria) on neuromuscular transmission. Toxicon. 1997; 35: 1275-1289.
33. Faltermann S, Zucchi S, Kohler E, Blom JF, Pernthaler J, Fent K. Molecular effects of the cyanobacterial toxin cyanopeptolin (CP1020) occurring in algal blooms: Global transcriptome analysis in zebrafish embryos. Aqua Toxicol. 2014; 149: 33-39.
34. Sivonen K, Jones G. Cyanobacterial toxins. In: Toxic cyanobacteria in water: A guide for their public health consequences, monitoring and management. 1st ed. London: E and FN Spon; 1999. pp. 41-111.
35. Stewart I, Schluter PJ, Shaw GR. Cyanobacterial lipopolysaccharides and human health-a review. Environ Health. 2006; 5: 7.
36. Sivonen K, Himberg K, Luukkainen R, Niemelä SI, Poon GK, Codd GA. Preliminary characterization of neurotoxic cyanobacteria blooms and strains from Finland. Toxic Assess. 1989; 4: 339-352.
37. Testai E, Scardala S, Vichi S, Buratti FM, Funari E. Risk to human health associated with the environmental occurrence of cyanobacterial neurotoxic alkaloids anatoxins and saxitoxins. Crit Rev Toxicol. 2016; 46: 385-419.
38. Campos F, Durán R, Vidal L, Faro LRF, Alfonso M. In vivo effects of the anatoxin-a on striatal dopamine release. Neuroch Res. 2006; 31: 491-501.
39. Borges HL, Branco LH, Martins MD, Lima CS, Barbosa PT, Lira GA, et al. Cyanotoxin production and phylogeny of benthic cyanobacterial strains isolated from the northeast of Brazil. Harmful Algae. 2015; 43: 46-57.
40. Foss AJ, Phlips EJ, Yilmaz M, Chapman A. Characterization of paralytic shellfish toxins from Lyngbya wollei dominated mats collected from two Florida springs. Harmful Algae. 2012; 16: 98-107.
41. Ongley SE, Pengelly JJL, Neilan BA. Elevated Na+ and pH influence the production and transport of saxitoxin in the cyanobacteria Anabaena circinalis AWQC131C and Cylindrospermopsis raciborskii T3. Environ Microbiol. 2016; 18: 427-438.
42. Kellmann R, Kaan Mihali T, Jae Jeon Y, Pickford R, Pomati F, Neilan BA. Biosynthetic intermediate analysis and functional homology reveal a Saxitoxin gene cluster in cyanobacteria. Appl Environ Microbiol. 2008; 74: 4044-4053.
43. Lage S, Costa PR, Moita T, Eriksson J, Rasmussen U, Rydberg SJ. BMAA in shellfish from two Portuguese transitional water bodies suggests the marine dinoflagellate Gymnodinium catenatum as a potential BMAA source. Aquat Toxicol. 2014; 152: 131-138.
44. Banack SA, Cox PA. Biomagnification of cycad neurotoxins in flying foxes: Implications for ALS-PDC in Guam. Neurology. 2003; 61: 387-389.
45. Briand JF, Jacquet S, Bernard C, Humbert JF. Health hazards for terrestrial vertebrates from toxic cyanobacteria in surface water ecosystems. Vet Res. 2003; 34: 361-377.
46. Malbrouck C, Kestemont P. Effects of microcystins on fish. Environ Toxicol Chem. 2006; 25: 72-86.

47. Huisman J; Hulot FD. Population dynamics of harmful cyanobacteria. In: Harmful cyanobacteria. Dordrecht: Springer; 2005. pp. 143-176.
48. Manganelli M, Stefanelli M, Vichi S, Andreani P, Nascetti G, Scialanca F, et al. Cyanobacteria biennal dynamic in a volcanic mesotrophic lake in central Italy: Strategies to prevent dangerous human exposures to cyanotoxins. Toxicon. 2016; 115: 28-40.
49. Zimba PV, Khoo L, Gaunt PS, Brittain S, Carmichael WW. Confirmation of catfish, Ictalurus punctatus (Rafinesque), mortality from Microcystis toxins. J Fish Dis. 2001; 24: 41-47.
50. Rantala A, Fewer DP, Hisbergues M, Rouhiainen L, Vaitomaa J, Börner T, et al. Phylogenetic evidence for the early evolution of microcystin synthesis. Proc Natl Acad Sci. 2004; 101: 568-573.
51. Keliri E, Paraskeva C, Sofokleous A, Sukenik A, Dziga D, Chernova E, et al. Occurrence of a single-species cyanobacterial bloom in a lake in Cyprus: Monitoring and treatment with hydrogen peroxide-releasing granules. Environ Sci Eur. 2021; 33: 31.
52. Krishnamurthy T, Carmichael WW, Sarver EW. Toxic peptides from freshwater cyanobacteria (blue-green algae). Isolation, purification and characterization of peptides from Microcystis aeruginosa and Anabaena flos-aquae. Toxicon. 1986; 24: 865-873.
53. Sivonen K, Namikoshi M, Evans WR, Carmichael WW, Sun F, Rouhiainen L, et al. Isolation and characterization of a variety of microcystins from seven strains of the cyanobacterial genus Anabaena. Appl Environ Microbiol. 1992; 58: 2495-2500.
54. Halinen K, Jokela J, Fewer DP, Wahlsten M, Sivonen K. Direct evidence for production of microcystins by Anabaena strains from the Baltic Sea. Appl Environ Microbiol. 2007; 73: 6543-6550.
55. Masango MG, Myburgh JG, Labuschagne L, Govender D, Bengis RG, Naicker D. Assessment of Microcystis bloom toxicity associated with wildlife mortality in the Kruger national park, South Africa. J Wildl Dis. 2010; 46: 95-102.
56. Meriluoto J, Blaha L, Bojadzija G, Bormans M, Brient L, Codd GA, et al. Toxic cyanobacteria and cyanotoxins in European waters - recent progress achieved through the CYANOCOST action and challenges for further research. Adv Oceanogr Limnol. 2017; 8: 144-161.
57. Stal LJ, Albertano P, Bergman B, von Bröckel K, Gallon JR, Hayes PK, et al. BASIC: Baltic Sea cyanobacteria. An investigation of the structure and dynamics of water blooms of cyanobacteria in the Baltic Sea-responses to a changing environment. Cont Shelf Res. 2003; 23: 1695-1714.
58. Moffitt MC, Neilan BA. Characterization of the nodularin synthetase gene cluster and proposed theory of the evolution of cyanobacterial hepatotoxins. Appl Environ Microbiol. 2004; 70: 6353-6362.
59. Hawkins PR, Runnegar MT, Jackson AR, Falconer I. Severe hepatotoxicity caused by the tropical cyanobacterium (blue-green alga) Cylindrospermopsis raciborskii (Woloszynska) Seenaya and Subba Raju isolated from a domestic water supply reservoir. Appl Environ Microbiol. 1985; 50: 1292-1295.
60. Banker R, Carmeli S, Hadas O, Teltsch B, Porat R, Sukenik A. Identification of cylindrospermopsin in Aphanizomenon ovalisporum (Cyanophyceae) isolated from lake Kinneret, Israel. J Phycol. 1997; 33: 613-616.

61. Preußel K, Stüken A, Wiedner C, Chorus I, Fastner J. First report on cylindrospermopsin producing Aphanizomenon flos-aquae (Cyanobacteria) isolated from two German lakes. Toxicon. 2006; 47: 156-162.
62. Neumann C, Bain P, Shaw G. Studies of the comparative in vitro toxicology of the cyanobacterial metabolite deoxycylindrospermopsin. J Toxicol Environ Health. 2007; 70: 1679-1686.
63. Mohamed ZA, Al-Shehri AM. Assessment of cylindrospermopsin toxin in an arid Saudi lake containing dense cyanobacterial bloom. Environ Monit Assess. 2013; 185: 2157-2166.
64. Dziga D, Kokocinski M, Maksylewicz A, Czaja-Prokop U, Barylski J. Cylindrospermopsin biodegradation abilities of Aeromonas sp. isolated from Rusałka lake. Toxins. 2016; 8: 55.
65. Rücker J, Stüken A, Nixdorf B, Fastner J, Chorus I, Wiedner C. Concentrations of particulate and dissolved cylindrospermopsin in 21 Aphanizomenon-dominated temperate lakes. Toxicon. 2007; 50: 800-809.
66. Buratti FM, Manganelli M, Vichi S, Stefanelli M, Scardala S, Testai E, et al. Cyanotoxins: Producing organisms, occurrence, toxicity, mechanism of action and human health toxicological risk evaluation. Arch Toxicol. 2017; 91: 1049-1130.
67. Durai P, Batool M, Choi S. Structure and effects of cyanobacterial lipopolysaccharides. Mar Drugs. 2015; 13: 4217-4230.
68. Bláhová L, Adamovský O, Kubala L, Švihálková Šindlerová L, Zounková R, Bláha L. The isolation and characterization of lipopolysaccharides from Microcystis aeruginosa, a prominent toxic water bloom forming cyanobacteria. Toxicon. 2013; 76: 187-196.
69. Wurtsbaugh WA, Paerl HW, Dodds WK. Nutrients, eutrophication and harmful algal blooms along the freshwater to marine continuum. Wiley Interdiscip Rev Water. 2019; 6: e1373.
70. Paerl HW, Huisman J. Climate change: A catalyst for global expansion of harmful cyanobacterial blooms. Eviron Microb Rep. 2009; 1: 27-37.
71. Downing JA, Watson SB, McCauley E. Predicting cyanobacteria dominance in lakes. Can J Fish Aquat Sci. 2001; 58: 1905-1908.
72. Whitton BA, Grainger SLJ, Hawley GRW, Simon JW. Cell-bound and extracellular phosphatase activities of cyanobacterial isolates. Microb Ecol. 1991; 21: 85-98.
73. Healey FP. Phosphate. In: The biology of cyanobacteria. Berkeley: University of California Press; 1982. pp. 105-124.
74. Davis TW, Harke MJ, Marcoval MA, Goleski J, Orano-Dawson C, Berry DL, et al. Effects of nitrogenous compounds and phosphorus on the growth of toxic and non-toxic strains of Microcystis during bloom events. Aquat Microb Ecol. 2010; 61: 149-162.
75. Kolowith LC, Ingall ED, Benner R. Composition and cycling of marine organic phosphorus. Limnol Oceanogr. 2001; 46: 309-320.
76. Kustka A, Sañudo-Wilhelmy S, Carpenter EJ, Capone DG, Raven, JA. A revised estimate of the iron use efficiency of nitrogen fixation, with special reference to the marine cyanobacterium Trichodesmium spp. (Cyanophyta). J Phycol. 2003; 39: 12-25.
77. Robarts RD, Zohary T. Temperature effects on photosynthetic capacity, respiration, and growth rates of bloom-forming cyanobacteria. N Z J Mar Freshw Res. 1987; 21: 391-399.
78. Briand J-F, Leboulanger C, Humbert J-F. Cylindrospermopsis raciborskii (Cyanobacteria) invasion at mid-latitudes: Selection, wide physiological tolerance, or global warming. J Phycol. 2004; 40: 231-238.

79. Capone DG, Zehr JP, Paerl HW, Bergman B, Carpenter EJ. Trichodesmium, a globally significant marine cyanobacterium. Science. 1997; 276: 1221-1229.
80. Ramos AG, Martel A, Codd GA, Soler E, Coca J, Rdo A, et al. Bloom of the marine diazotrophic cyanobacterium Trichodesmium erythraeum in the Northwest African Upwelling. Mar Ecol Prog Ser. 2005; 301: 303-305.
81. Murrell MC, Lores EM. Phytoplankton and zooplankton seasonal dynamics in a subtropical estuary: Importance of cyanobacteria. J Plank Res. 2004; 26: 371-382.
82. O'Neil J, Dennison WC. Lyngbya majuscula in Southeast Queensland waterways. In: Healthy waterways - healthy catchments. Brisbane, Australia: South East Queensland, Regional Water Quality Strategy, Brisbane City Council; 2005. pp. 119-148.
83. Paul VJ, Thacker RW, Banks K, Golubic S. Benthic cyanobacterial bloom impacts on the reefs of South Florida (Broward County, USA). Coral Reefs. 2005; 24: 693-697.
84. Watkinson AJ, O'Neil JM, Dennison WC. Ecophysiology of the marine cyanobacterium Lyngbya majuscula (Oscillatoriaceae) in Moreton Bay, Australia. Harmful Algae. 2005; 4: 697-715.
85. Richardson LL, Kuta KG. Ecological physiology of the black band disease cyanobacterium Phormidium corallyticum. FEMS Microbiol Ecol. 2003; 43: 287-298.
86. Rapala J, Sivonen K, Lyra C, Niemela SI. Variation of microcystins, cyanobacterial hepatoxins, in Anabaena spp. as a function of growth stimuli. Appl Environ Microbiol. 1997; 63: 2206-2212.
87. Wiedner C, Visser PM, Fastner J, Metcalf JS, Codd GA, Mur LR. Effects of light on the microcystin content of Microcystis strain PCC 7806. Appl Env Microbiol. 2003; 69: 1475-1481.
88. Tonk L, Visser PM, Christiansen G, Dittmann E, Snelder EOFM, Wiedner C, et al. The microcystin composition of the cyanobacterium Planktothrix agardhii changes toward a more toxic variant with increasing light intensity. App Env Microbiol. 2005; 71: 5177-5181.
89. Paul VJ. Global warming and cyanobacterial harmful algal blooms. In: Cyanobacterial harmful algal blooms: State of the science and research needs. New York: Springer; 2008. pp. 239-257.
90. Verspagen JM, Van de Waal DB, Finke JF, Visser PM, Van Donk E, Huisman J. Rising CO2 levels will intensify phytoplankton blooms in eutrophic and hypertrophic lakes. PLOS One. 2014; 9: e104325.
91. Burnap RL, Hagemann M, Kaplan A. Regulation of CO2 concentrating mechanism in cyanobacteria. Life. 2015; 5: 348-371.
92. Sandrini G, Matthijs HCP, Verspagen JMH, Muyzer G, Huisman J. Genetic diversity of inorganic carbon uptake systems causes variation in CO2 response of the cyanobacterium Microcystis. ISME J. 2014; 8: 589-600.
93. Low-Décarie E, Fussmann GF, Bell G. The effect of elevated CO2 on growth and competition in experimental phytoplankton communities. Glob Change Biol. 2011; 17: 2525-2535.
94. Hutchins DA, Fu FX, Webb EA, Walworth N, Tagliabue A. Taxon-specific response of marine nitrogen fixers to elevated carbon dioxide concentrations. Nat Geosci. 2013; 6: 790-795.
95. Sandrini G, Ji X, Verspagen JMH, Tann RP, Slot PC, Luimstra VM, et al. Rapid adaptation of harmful cyanobacteria to rising CO2. Proc Natl Acad Sci. 2016; 113: 9315-9320.
96. Ji X, Verspagen JMH, Stomp M, Huisman J. Competition between cyanobacteria and green algae at low versus elevated CO2: Who will win, and why? J Exp Bot. 2017; 68: 3815-3828.
97. Visser PM, Ibelings BW, Bormans M, Huisman J. Artificial mixing to control cyanobacterial blooms: A review. Aquat Ecol. 2016; 50: 423-441.

98. Stewart I, Webb PM, Schluter PJ, Shaw GR. Recreational and occupational field exposure to freshwater cyanobacteria-a review of anecdotal and case reports, epidemiological studies and the challenges for epidemiologic assessment. Environ Health. 2006; 5: 6.
99. Plaas HE, Paerl HW. Toxic cyanobacteria: A growing threat to water and air quality. Environ Sci Technol. 2020; 55: 44-64.
100. Hudnell HK, Dortch Q. A synopsis of research needs identified at the interagency, international symposium on cyanobacterial harmful algal blooms (ISOC-HAB). In: Cyanobacterial harmful algal blooms: State of the science and research needs. New York: Springer; 2008. pp 17-43.
101. Poniedziałek B, Rzymski P, Wiktorowicz K. Toxicity of cylindrospermopsin in human lymphocytes: Proliferation, viability and cell cycle studies. Toxicol In Vitro. 2014; 28: 968-974.
102. Poniedziałek B, Rzymski P, Karczewski J. The role of the enzymatic antioxidant system in cylindrospermopsin-induced toxicity in human lymphocytes. Toxicol In Vitro. 2015; 29: 926-932.
103. Poniedziałek B, Rzymski P, Karczewski J. Cylindrospermopsin decreases the oxidative burst capacity of human neutrophils. Toxicon. 2014; 87: 113-119.
104. Reisner M, Carmeli S, Werman M, Sukenik A. The cyanobacterial toxin cylindrospermopsin inhibits pyrimidine nucleotide synthesis and alters cholesterol distribution in mice. Toxicol Sci. 2004; 82: 620-627.
105. Lankoff A, Wojcik A, Lisowska H, Bialczyk J, Dziga D, Carmichael WW. No induction of structural chromosomal aberrations in cylindrospermopsin-treated CHO-K1 cells without and with metabolic activation. Toxicon. 2007; 50: 1105-1115.
106. Griffiths DJ, Saker ML. The palm island mystery disease 20 years on: A review of research on the cyanotoxin cylindrospermopsin. Environ Toxicol. 2003; 18: 78-93.
107. Sieroslawska A, Rymuszka A, Adaszek Ł. Effects of cylindrospermopsin on the phagocytic cells of the common carp (Cyprinus carpio L.). J Appl Toxicol. 2015; 35: 1406-1414.
108. Ufelmann H, Krüger T, Luckas B, Schrenk D. Human and rat hepatocyte toxicity and protein phosphatase 1 and 2A inhibitory activity of naturally occurring desmethyl-microcystins and nodularins. Toxicol. 2012; 293: 59-67.
109. Meili M, Kutz A, Briel M, Christ-Crain M, Bucher HC, Mueller B, et al. Infection biomarkers in primary care patients with acute respiratory tract infections-comparison of procalcitonin and C-reactive protein. BMC Pulm Med. 2016; 16: 1-9.
110. Lankoff A, Sochacki J, Spoof L, Meriluoto J, Wojcik A, Wegierek A, et al. Nucleotide excision repair impairment by nodularin in CHO cell lines due to ERCC1/XPF inactivation. Toxicol Lett. 2008; 179: 101-107.
111. Ufelmann H, Schrenk D. Nodularin-triggered apoptosis and hyperphosphorylation of signaling proteins in cultured rat hepatocytes. Toxicol In Vitro. 2015; 29: 16-26.
112. Persson K-J, Legrand C, Olsson T. Detection of nodularin in European flounder (Platichthys flesus) in the west coast of Sweden: Evidence of nodularin mediated oxidative stress. Harmful Algae. 2009; 8: 832-838.
113. Wiese M, D'Agostino PM, Mihali TK, Moffitt MC, Neilan BA. Neurotoxic alkaloids: Saxitoxin and its analogs. Mar Drugs. 2010; 8: 2185-2211.
114. Adeymo OM, Sirén A-L. Cardio-respiratory changes and mortality in the conscious rat induced by (+)- and (±)-anatoxin-a. Toxicon. 1992; 30: 899-905.

115. Orjala J, Nagle DG, Hsu V, Gerwick WH. Antillatoxin: An exceptionally ichthyotoxic cyclic lipopeptide from the tropical cyanobacterium Lyngbya majuscula. J Am Chem Soc. 1995; 117: 8281-8282.
116. Wu M, Okino T, Nogle LM, Marquez BL, Williamson RT, Sitachitta N, et al. Structure, synthesis, and biological properties of kalkitoxin, a novel neurotoxin from the marine cyanobacterium Lyngbya majuscula. J Am Chem Soc. 2000; 122: 12041-12042.
117. Chen L, Chen J, Zhang X, Xie P. A review of reproductive toxicity of microcystins. J Hazard Mater. 2016; 301: 381-399.
118. Facciponte DN, Bough MW, Seidler D, Carroll JL, Ashare A, Andrew AS, et al. Identifying aerosolized cyanobacteria in the human respiratory tract: A proposed mechanism for cyanotoxin-associated diseases. Sci Total Environ. 2018; 645: 1003-1013.
119. Brózman O, Kubickova B, Babica P, Laboha P. Microcystin-LR does not alter cell survival and intracellular signaling in human bronchial epithelial cells. Toxins. 2020; 12: 165.
120. Yuan G, Xie P, Zhang X, Tang R, Gao Y, Li D, et al. In vivo studies on the immunotoxic effects of microcystins on rabbit. Environ Toxicol. 2012; 27: 83-89.
121. Nonga HE, Sandvik M, Miles CO, Lie E, Mdegela RH, Mwamengele GL, et al. Possible involvement of microcystins in the unexplained mass mortalities of lesser flamingo (Phoeniconaias minor Geoffroy) at lake Manyara in Tanzania. Hydrobiologia. 2011; 678: 167-178.
122. Lopez-Rodas V, Maneiro E, Lanzarot MP, Perdigones N, Costas E A Mass wildlife mortality due to cyanobacteria in the Doñana National Park, Spain Vet Rec. 2008; 162: 317-318.
123. Choi SH, Kim SG. Lipopolysaccharide inhibition of rat hepatic microsomal epoxide hydrolase and glutathione S-transferase gene expression irrespective of nuclear factor-kB activation. Biochem Pharmacol. 1998; 56: 1427-1436.
124. Wiegand C, Pflugmacher S. Ecotoxicological effects of selected cyanobacterial secondary metabolites. Toxicol Appl Pharmacol. 2005; 203: 201-218.
125. Glover WB, Mash DC, Murch SJ. The natural non-protein amino acid N-β-methylamino-L-alanine (BMAA) is incorporated into protein during synthesis. Amino Acids. 2014; 46: 2553-2559.
126. Louati I, Pascault N, Debroas D, Bernard C, Humbert JF, Leloup J. Structural diversity of bacterial communities associated with bloom-forming freshwater cyanobacteria differs according to the cyanobacterial genus. PLOS One. 2015; 10: e0140614.
127. Berg C, Dupont CL, Asplund-Samuelsson J, Celepli NA, Eiler A, Allen AE, et al. Dissection of microbial community functions during a cyanobacterial bloom in the Baltic Sea via metatranscriptomics. Front Mar Sci. 2018; 5: doi. 10 3389/fmars.2018.00055.
128. Shao K, Zhang L, Wang Y, Yao X, Tang X, Qin B, et al. The responses of the taxa composition of particle-attached bacterial community to the decomposition of Microcystis blooms. Sci Total Environ. 2014; 488-489: 236-242.
129. Kahru M, Leppanen JM, Rud O. Cyanobacterial blooms cause heating of the sea surface. Mar Ecol Prog Ser. 1993; 101: 1-7.
130. Ibelings BW, Vonk M, Los HFJ, van der Molen DT, Mooij WM. Fuzzy modeling of cyanobacterial surface waterblooms: Validation with NOAA-AVHRR satellite images. Ecol Appl. 2003; 13: 1456-1472.

131. Siqueira DB, Oliveira-Filho EC. Cianobactérias de água doce e saúde pública: Uma revisão. Universitas: Ciências da Saúde. 2005; 3: 109-127.
132. Wiegand C, Pflugmacher S. Ecotoxicological effects of selected cyanobacterial secondary metabolites: A short review. Toxicol Appl Pharmacol. 2005; 203: 201-218.
133. Rohrlack T, Christoffersen K, Dittmann E, Nogueira I, Vasconcelos V, Börner T. Ingestion of microcystins by Daphnia: Intestinal uptake and toxic effects. Limnol Oceanogr. 2005; 50: 440-448.
134. Chen W, Song L, Ou D, Gan N. Chronic toxicity and responses of several important enzymes in Daphnia magna on exposure to sublethal microcystin-LR. Environ Toxicol. 2005; 20: 323-330.
135. Singh DP, Tyagi MB, Kumar A, Thakur JK, Kumar A. Antialgal activity of a hepatotoxin-producing cyanobacterium, Microcystis aeruginosa. World J Microbiol Biotechnol. 2001; 17: 15-22.
136. Suikkanen S, Fistarol GO, Granéli E. Allelopathic effects of the Baltic cyanobacteria Nodularia spumigena, Aphanizomenon flos-aquae and Anabaena lemmermannii on algal monocultures. J Exp Mar Biol Ecol. 2004; 308: 85-101.
137. Pflugmacher S. Possible allelopathic effects of cyanotoxins, with reference to microcystin-LR, in aquatic ecosystems. Environ Toxicol. 2002; 17: 407-413.
138. Gérard C, Brient L, Le Rouzic B. Variation in the response of juvenile and adult gastropods (Lymnaea stagnalis) to cyanobacterial toxin (microcystin-LR). Environ Toxicol. 2005; 20: 592-596.
139. Juhel G, Davenport J, O'halloran J, Culloty SC, O'riordan RM, James KF, et al. Impacts of microcystins on the feeding behaviour and energy balance of zebra mussels, Dreissena polymorpha: A bioenergetics approach. Aquat Toxicol. 2006; 79: 391-400.
140. Nogueira ICG, Pereira P, Dias E, Pflugmacher S, Wiegand C, Franca S, et al. Accumulation of paralytic shellfish toxins (PST) from the cyanobacterium Aphanizomenon issatschenkoi by the cladoceran Daphnia magna. Toxicon. 2004; 44: 773-780.
141. Costa SM. Efeitos de Saxitoxinas Produzidas por Cylindrospermopsis raciborskii e de Outras Cianotoxinas Sobre Cladóceros (Branchiopoda). Rio de Janeiro, Brazil: Federal University of Rio de Janeiro; 2005.
142. Liu Y, Song L, Li X, Liu T. The toxic effects of microcystin-LR on embryo-larval and juvenile development of loach, Misguruns mizolepis Gunthe. Toxicon. 2002; 40: 395-399.
143. Oberemm A, Becker J, Codd GA, Steinberg C. Effects of cyanobacterial toxins and aqueous crude extracts of cyanobacteria on the development of fish and amphibians. Environ Toxicol. 1999; 14: 77-88.
144. Ferrão-Filho AS, Cunha R, Magalhães VF, Soares MC, Baptista DF. Evaluation of sub-lethal toxicity of cyanobacteria on the swimming activity of aquatic organisms by image analysis. J Braz Soc Ecotoxicol. 2007; 2: 93-100.
145. Lefebvre KA, Elder NE, Hershberger PK, Trainer VL, Stehr CM, Scholz NL. Dissolved saxitoxin causes transient inhibition of sensorimotor function in larval Pacific herring (Clupea harengus pallasi). Marine Biol. 2005; 147: 1393-1402.
146. Oberemm A, Fastner J, Steinberg CEW. Effects of MC-LR and cyanobacterial crude extracts on embryo-larval development of zebrafish. Water Res. 1997; 31: 2918-2921.

147. Jacquet C, Thermes V, de Luze A, Puiseux-Dao S, Bernard C, Joly JS, et al. Effects of microcystin-LR on development of medaka fish embryos (Oryzias latipes). Toxicon. 2004; 43: 141-147.
148. Ernst B, Hitzfeld B, Dietrich D. Presence of Planktothrix sp. and cyanobacterial toxins in Lake Ammersee, Germany and their impact on whitefish (Coregonus lavaretus L.). Environ Toxicol. 2001; 16: 483-488.
149. Palikova M, Navratil S, Marsalek B, Blaha L. Toxicity of crude extract of cyanobacteria for embryos and larvae of carp (Cyprinus carpio L.). Acta Vet Brno. 2003; 72: 437-443.
150. Jeppesen E, Søndergaard M, Jensen JP, Havens KE, Anneville O, Carvalho L, et al. Lake responses to reduced nutrient loading-an analysis of contemporary long-term data from 35 case studies. Freshwater Boil. 2005; 50: 1747-1771.
151. Fastner J, Abella S, Litt A, Morabito G, Vörös L, Pálffy K, et al. Combating cyanobacterial proliferation by avoiding or treating inflows with high P load—experiences from eight case studies. Aquat Ecol. 2016; 50: 367-383.
152. Søndergaard M, Jensen JP, Jeppesen E. Role of sediment and internal loading of phosphorus in shallow lakes. Hydrobiologia. 2003; 506: 135-145.
153. Ibelings BW, Portielje R, Lammens EHRR, Noordhuis R, van den Berg MS, Joosse W, et al. Resilience of alternative stable states during the recovery of shallow lakes from eutrophication: Lake Veluwe as a case study. Ecosystems. 2007; 10: 4-16.
154. Lürling M, Faassen EJ. Controlling toxic cyanobacteria: Effects of dredging and phosphorus binding clay on cyanobacteria and microcystins. Water Res. 2012; 46: 1447-1459.
155. Copetti D, Finsterle K, Marziali L, Stefani F, Tartari G, Douglas G, et al. Eutrophication management in surface waters using lanthanum modified bentonite: A review. Water Res. 2016; 97: 162-74.
156. Paerl HW, Gardner WS, Havens KE, Joyner AR, McCarthy MJ, Newell SE, et al. Mitigating cyanobacterial harmful algal blooms in aquatic ecosystems impacted by climate change and anthropogenic nutrients. Harmful Algae. 2016; 54: 213-222.
157. Huisman J, Sharples J, Stroom JM, Visser PM, Kardinaal WE, Verspagen JMH, et al. Changes in turbulent mixing shift competition for light between phytoplankton species. Ecol. 2004; 85: 2960-2970.
158. Mitrovic SM, Hardwick L, Dorani F. Use of flow management to mitigate cyanobacterial blooms in the Lower Darling River, Australia. J Plankton Res. 2011; 33: 229-241.
159. Matthijs HCP, Jančula D, Visser PM, Maršálek B. Existing and emerging cyanocidal compounds: New perspectives for cyanobacterial bloom mitigation. Aquat Ecol. 2016; 50: 443-460.
160. Matthijs HCP, Visser PM, Reeze B, Meeuse J, Slot PC, Wijn G, et al. Selective suppression of harmful cyanobacteria in an entire lake with hydrogen peroxide. Water Res. 2012; 46: 1460-1472.
161. Gerphagnon M, Macarthur DJ, Latour D, Gachon CMM, Van Ogtrop F, Gleason FH, et al. Microbial players involved in the decline of filamentous and colonial cyanobacterial blooms with a focus on fungal parasitism. Environ Microbiol. 2015;17: 2573-2587.
162. Huisman J, Codd GA, Paerl HW, Ibelings BW, Verspagen JMH, Visser PM. Cyanobacterial blooms. Nat Rev Microbiol. 2018; 16: 471-483.

163. Van Wichelen J, Vanormelingen P, Codd GA, Vyverman W. The common bloom-forming cyanobacterium Microcystis is prone to a wide array of microbial antagonists. Harmful Algae. 2016; 55: 97-111.
164. Coloma SE, Dienstbier A, Bamford DH, Sivonen K, Roine E, Hiltunen T. Newly isolated Nodularia phage influences cyanobacterial community dynamics. Environ Microbiol. 2017; 19: 273-286.
165. Waajen GWAM, Van Bruggen NCB, Pires LMD, Lengkeek W, Lürling M. Biomanipulation with quagga mussels (Dreissena rostriformis bugensis) to control harmful algal blooms in eutrophic urban ponds. Ecol Eng. 2016; 90: 141-150.
166. White JD, Sarnelle O. Size-structured vulnerability of the colonial cyanobacterium, Microcystis aeruginosa, to grazing by zebra mussels (*Dreissena polymorpha*). Freshwater Biol. 2014; 59: 514-525.
167. Conroy JD, Kane DD, Dolan DM, Edwards WJ, Charlton MN, Culver DA. Temporal trends in Lake Erie plankton biomass: Roles of external phosphorus loading and dreissenid mussels. J Great Lakes Res. 2005; 31: 89-110.
168. Sarnelle O, White JD, Horst GP, Hamilton SK. Phosphorus addition reverses the positive effect of zebra mussels (Dreissena polymorpha) on the toxic cyanobacterium, *Microcystis aeruginosa*. Water Res. 2012; 46: 3471-3478.
169. Søndergaard M, Jeppesen E, Lauridsen TL, Skov C, Van Nes EH, Roijackers R, et al. Lake restoration: Successes, failures and long-term effects. J Appl Ecol. 2007; 44: 1095-1105.
170. Søndergaard M, Lauridsen TL, Johansson LS, Jeppesen E. Repeated fish removal to restore lakes: Case study of Lake Væng, Denmark—two biomanipulations during 30 years of monitoring. Water. 2017; 9: 43.
171. Paerl HW, Otten TG. Harmful cyanobacterial blooms: causes, consequences, and controls. Microb Ecol. 2013; 65: 995-1010.