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Potential implications of cyanotoxin on aqua feed efficiency: It's mode of action and mitigation strategies

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Abstract
The use of aquafeed in semi-intensive and intensive culture practices has raised several issues, like high organic load and altered nutrients in the culture environment, effluent to the natural aquatic ecosystem, the prevalence of diseases, and altered water quality parameters eutrophication, etc. and finally leading undesired heavy algal bloom. Later, the system triggers a chain of issues such as reduced dissolved oxygen level, diurnal fluctuation of fundamental water quality parameters, and stress to the culture animals. The situation aggravates when such blooms are caused or dominated by cyanotoxin-rich blue-green algae and have a harmful impact on fish physiology. The sub-lethal levels of cyanotoxins may reduce growth and alter feed performance efficiency. Therefore, the cumulative impact of reduced dissolved oxygen, altered fundamental water quality parameters, and presence of cyanotoxins even at the sublethal level may result in poor feed performance. The cyanobacterial blooms can look like foam, scum, or mats in culture ponds and may float on the surface or near dyke of the water's surface. According to their toxicological targets, cyanotoxins are classified as hepatotoxins (microcystins, nodularins, cylindrospermopsin), neurotoxins (anatoxin-a, saxitoxins), dermatotoxin (irritants), cytotoxins (aplysiatoxin, *Lyngbya*toxin-a), and endotoxins (irritants) (lipopolysaccharides). The implementation of effective mitigation strategies such as chemical, biological, and farmer's awareness approaches may be the most realistic; however, the nutritional measure to overcome the aquaculture incidence of cyanobacterial bloom and associated lethal and sub-lethal impact in aquaculture needs special attention in relation on the impact on growth and feed efficiency.

Keywords: Cyanotoxins, aquafeed, feed efficiency, mode of action, mitigation strategy

Introduction
Aquaculture and aquatic resources are being foreseen as the future supplier of quality food for humans. The average growth rate of global aquaculture production for the last four decades has been around 6% (www.fao.org/fishery/topic/16140/en), which is the highest among all food production sectors globally. Such impressive growth has been due to technological intervention in culture practices, and the use of more commercial species in culture. However, the core input, the feed, is the most determining factor for production and better growth in all culture practices. The fish feed accounts almost 60-70% of the total input cost in aquaculture. Therefore, in feed-based aquaculture, several interventions have been made to improve the product's feed efficiency and cost-effectiveness. But the use of the feed-in aquaculture practices, especially the intensive and semi-intensive practices, has raised cascading issues, such as organic load and altered nutrient in the culture environment, the effluent from aquaculture to the natural environment and its impact on the aquatic ecosystem, the prevalence of diseases, altered water quality parameter, eutrophication leading heavy algal bloom in culture systems.

The algal blooms are mostly of undesired nature. If so, it triggers a chain of the issue in the system, such as a reduced dissolved oxygen level, diurnal fluctuation of fundamental water quality parameters, and stress to the culture animals. The situation aggravates when such blooms are caused or dominated by cyanotoxin-rich blue-green algae as the cyanotoxin give deleterious impact on fish physiology. So even at sub-lethal levels, such moieties may reduce growth and alter feed performance efficiency. Therefore, the cumulative impact of reduced dissolved oxygen, altered fundamental water quality parameters, and presence of cyanotoxins even at the sublethal level may together result in poor feed performance.

Cyanotoxins are a broad collection of natural poisons in terms of both chemical and toxicological properties. Despite their aquatic origins, most of the cyanotoxins discovered far appear to be more dangerous to terrestrial mammals than aquatic species—the aquatic biota.

Cyanobacteria create a wide range of unique metabolites found in nature. The purpose of which is unknown; however, some, may be unintentionally, induce consequences depending on other biotas in the aquatic system, including fish. The majority of most of the articles have been on chemicals that have an effect on toxins, and pharmaceutically beneficial compounds have been found in humans and cattle. Further, cyanobacteria and the biochemical process produce a variety of non-toxic compounds and their pharmacological characteristics are entirely unknown.

In freshwater ecosystems, the abundant growth of cyanobacteria has increased due to high levels of anthropogenic nutrients (eutrophication) and global climate change that has created a severe concern about harmful algal bloom formation. In the aquaculture system and its effluents, the feed-based organic and nutrient load has been responsible for cyanobacterial growth. Such blooms can look like foam, scum, or mats in culture ponds and may float on the surface or near dyke on the water's surface inside due to the aerator's water activity. But they are not always visible. Nor are such blooms always green; they can be blue, and some cyanobacteria species are colored brownish-red. The water can smell bad when the cyanobacterial bloom crash due to poor dissolved oxygen or the absence of one or more limiting nutrients.

Cyanobacteria in freshwater and marine habitats have been shown to produce a variety of poisonous secondary chemicals known as cyanotoxins. These toxic chemicals or compounds are hazardous to the survival of many aquatic species, wild and domestic animals, and people. Fishes and other aquatic creatures, including plants and animals and Phyto/zooplanktons that live in toxic bloom-rich habitats, are directly exposed to the damaging effects of various cyanotoxins. Intoxication in wild and domestic animals and people occurs due to either direct eating of toxin-producing cyanobacteria cells or intake of cyanotoxin-contaminated drinking water (Rastogi *et al.*, 2014) [55]. There are several cyanotoxins reported that cause deleterious physiological impact and even pathological signs on humans, terrestrial animals, and fishes.

Classification of toxic compounds from cyanobacteria

Cyanotoxins generated by freshwater cyanobacteria are categorized according to their sources, molecular structures, or adverse effects. According to their toxicological targets, they are classified as hepatotoxins (microcystins, nodularins, cylindrospermopsin), neurotoxins (anatoxin-a, anatoxin-a(s), saxitoxins), dermatotoxin (irritants), cytotoxins (aplysiatoxin, *Lyngbya*toxin-a), and endotoxins (irritants) (lipopolysaccharides) (Bláha *et al.*, 2009) [6], as listed in (Table 1).

Hepatotoxins

Microcystin: Microcystins are cyclic heptapeptides, and they are the most essential cyanotoxins based on their worldwide spread on health and water quality. Their structure has been identified as over 200 naturally occurring structural variants. It includes six amino acids (four non-protein and two protein) that form a ring structure: cyclo-(-D-Ala-L-X-D-MeAsp-L-Z-Adda-D-Glu-Mdha). One non-protein, termed as ADDA (3-amino-9-methoxy-2, 6, 8-trimethyl-10-phenyldeca-4, 6-dienoic acid), forms a side chain that can be used to quantify variant types of microcystin. Two protein L-amino acids at position 2 (leucine- X) and 4 (arginine- Z) contribute significantly to the structural variability (Sivonen and Jones, 1999; Massey *et al.*, 2018; Yang *et al.*, 2018a, b) [63, 79, 80]. More than 100 microcystin variants with varying degrees of toxicity have been identified from cyanobacterial blooms.

Among the most prevalent forms are microcystin LR, microcystin-RR, and microcystin-YR; as well as the X and Y, are indicated as Leucine (L), arginine (R), respectively and tyrosine is the Z variable amino acids (Puddick *et al.*, 2015; Yang *et al.*, 2018a, b) [53, 80] for microcystin-LR, microcystin-RR, and microcystin-YR (Y). Microcystin-LR is the most poisonous, well-studied, and widely used. It is a common variation and one of the most significant algae species toxins that have gotten a lot of attention worldwide (Zhou *et al.*, 2013; Massey *et al.*, 2018) [88, 79].

Mode of Action

When nutrient levels and climatic circumstances are favorable for heavy algal bloom (HAB) development, microcystins are regularly formed in the freshwater aquatic system and in aquaculture ponds. Toxin concentrations can reach hazardous levels of exceptionally high (Van der Merwe *et al.*, 2015) [7.], and it has quite high persistence (Harada *et al.*, 1996) [82] throughout the body. Microcystins are released from cyanobacterial cells after ingestion and absorbed into the small intestine's portal circulation via bile acid transporters.

The primary target cells for microcystins are in the liver and the intestinal lining. Microcystins are collected in the hepatocytes through bile acid transporters (organic anion-transporting polypeptides) comparable to those found on hepatocytes membranes (Hooser *et al.*, 1991) [26]. Microcystins cause irreversible damage or inhibit serine/threonine protein phosphatases (PPs), mainly 2A and 1 (Yoshizawa *et al.*, 1990) [82], leading to an increase in cell phosphorylated protein load and subsequent deregulation of fundamental cellular processes. Microcystin-LR might also bind to ATP synthase, causing hepatocyte apoptosis (Mikhailov *et al.*, 2003) [42].

Protein phosphatases (PPs) are ubiquitous and found in all tissues and species as varied as mammals, plants, and microorganisms. They play an essential function in the immune system. Protein phosphatases catalyze the reversal of kinase activity via hydrolytic elimination of the phosphoryl group from kinases. Protein phosphatases have a broad substrate specificity and play a variety of roles, and it is involved in the control of several cellular activities (Huang *et al.*, 2015; Zeng *et al.*, 2015) [27, 84]. Protein phosphatase 2A is a well-conserved enzyme, and it is a crucial inhibitor of active protein kinases in eukaryotic cells. Using this specific ability, microcystin-LR binds to tubulin and destabilizes microtubules (Komatsu *et al.*, 2007; Kaur, 2019) [36, 34], which induces apoptosis and cell damage.

Microcystins produce toxicity mainly through oxidative stress by alterations in cytotoxicity markers such as leakage of lactate dehydrogenase enzyme, lipid peroxidation, reactive oxygen species (ROS) generation, and antioxidant enzymes. Microcystin-LR also activates the c-Jun N-terminal kinase (JNK) pathway, one of the significant signaling cassettes of the mitogen-activated protein kinase (MAPK) signaling pathway. It affects enzymes involved in energy metabolism and mitochondrial malfunction, leading to hepatocyte death and oxidative liver damage. Microcystin-LR has been shown to produce intracellular (endosome) ROS that is demonstrated due to a calcium-mediated decrease of mitochondrial membrane potential. Microcystin-LR-mediated Oxidative

stress is characterized by a rise in hydroxyl radicals and the consequent activation of apoptosis-related genes p38, JNKa, and Bcl-2 genes in fish liver (Valério *et al.*, 2016; Kaur, 2019) [71, 34]. Therefore, toxic effects in hepatocytes and other live cells are diverse and include cytoskeleton disruption, DNA damage, and apoptosis. It's caused by mitochondrial damage, and oxidative stress-based production of free oxygen radicals (Zegura *et al.*, 2004; Ding and Nam Ong, 2003) [83, 18].

Cylindrospermopsin

Cylindrospermopsin is a polyketide alkaloid cyanotoxin produced by several freshwater cyanobacteria taxa, including *Cylindrospermopsis*, Aphanizomenon, Anabaena, and *Cylindrospermopsis*, Raphidiopsis, *Lyngbya*, and Umezakia (Guzmán-Guillén *et al.*, 2013) [21]. It may be found in surface freshwaters worldwide (De la Cruz *et al.*, 2013) [17]. Cylindrospermopsin is a zwitterionic, highly water-soluble molecule consisting of tricyclic guanidine coupled with hydroxymethyl uracil (Ohtani *et al.*, 1992) [48]. At present, according to Wimmer *et al.*, 2014 [76], there are five knowns structural variants of Cylindrospermopsin. Among them two known Variants: deoxycylindrospermopsin (Norris *et al.*, 1999) [47], which is relatively less toxic, and 7-epicyl-indrospermopsin (Banker *et al.*, 2001) [4], which is relatively more toxic, have been properly deleanted. Chiswell *et al.*, 1999 [47] found that cylindrospermopsin is resistant to high temperatures, sunshine, and pH extremes. Unlike microcystins, cylindrospermopsin is often discharged into the surrounding water by the cells (Rucker *et al.*, 2007) [56]. It bioaccumulates, particularly in aquatic environmental creatures at the bottom of the food chain, such as gastropods, crustaceans, and bivalves (Kinnear *et al.*, 2008) [89].

Mode of Action

The primary target tissue of purified cylindrospermopsin toxicosis is the liver and as well as kidney, thymus, and heart (Terao *et al.*, 1994) [68]. It is a potent inhibitor of protein synthesis in a concentration-dependent and irreversible manner, but the exact mechanism of action has not been fully described anywhere. However, this toxic compound shows four sequential phases of hepatocyte damage, including protein synthesis inhibition, membrane proliferation, lipid infiltration, and necrosis. Some necessary factors that influence the effects of this toxicity and those are DNA fragmentation *in vitro* and metabolic activation by a P-450 enzyme (Bazin *et al.*, 2010) [5]. Different studies show that crude extracts have a higher potential and a wide range of toxic effects than purified cylindrospermopsin (Shaw *et al.*, 2000; Seifert *et al.*, 2007) [61, 60].

Neurotoxins

Anatoxin: A

Anatoxin-A occurs in freshwater environments mostly, and it is a very potent and persistent neurotoxic compound. It is produced by the following freshwater genera, including Anabaena, Aphanizomenon, *Microcystis*, *Planktothrix*, Raphidiopsis, *Arthrospira*, *Cylindrospermum*, *Phormidium*, Nostoc, and Oscillatoria. (Osswald *et al.*, 2007 [50]. It is a bicyclic amine alkaloid that contains a homatropine scaffold from glutamic acid. A small amount of Homoanatoxin-aor methylene-anatoxin-a (a structural analog) has been extracted from Oscillatoria Formosa (Skulberg *et al.*, 1992) [64] and used in acetylcholine receptor research.

Mode of Action

Anatoxin-A is an acetylcholine receptor agonist with a 100-fold preference for nicotinic receptors over muscarinic receptors. It binds to the acetylcholine receptor in the same way that acetylcholine does (pre-synaptically and post-synaptically), resulting in sodium/potassium ion channels opening and causing a depolarizing response blockade (Aronstam and Witkop, 1981) [2]. The anatoxin is more potent than any other acetylcholine or nicotine. Anatoxin-a binding to nicotinic acetylcholine receptors at neuromuscular junctions, causes uncontrolled action potential propagation, which manifests clinically as uncoordinated muscle contraction, muscle fatigue, and finally, muscular paralysis. The cholinesterase enzyme does not degrade choline-anatoxin-a, resulting in chronic muscle stimulation (Wonnacott and Gallagher, 2006) [71].

Nicotinic receptor stimulation in the cardiovascular system leads to an increase in blood pressure and heart rate (Siren and Feurstein, 1990) [62]. Presynaptic nicotinic receptors stimulated by anatoxin-a in the nervous system may also result in dopamine release. For example, it acts as a neurotransmitter that could be influenced to make postsynaptic receptors more susceptible to overstimulation (Wonnacott and Gallagher, 2006) [71]. However, central nervous system receptors are less sensitive to anatoxin-a when compared to peripheral receptors (Aracava *et al.*, 1987) [1].

Anatoxin- a (s)

Anatoxin-a(s) is a natural organophosphate analog produced by Anabaena cyanobacteria. The (s) in anatoxin-a(s) refers to salivation, a common sign of poisoning observed in laboratory rodents after exposure. However, it has been reported in very few cases. It is a cyclic N-hydroxyguanine with a phosphate ester moiety with no structural variants and is very much susceptible to rapid degradation (Matsunaga *et al.*, 1989) [39]. Cyclic guanidine can act as an intermediate in the synthesis of anatoxin-a(s), as in pure forms (Moura and Pinto, 2010) [44].

Mode of Action

Anatoxin-a(s) is a noncompetitive acetylcholinesterase inhibitor (AChE). Anatoxin-a(s), like other organophosphate poisons, is activated through oxidative metabolism. AChE is required in hydrolysis for the inactivation of Ach at the sites of nicotinic and muscarinic receptors. As a result, the enzyme causes an increase in Ach levels at the receptor sites, triggering an overabundance of nicotinic and muscarinic receptors stimulation, resulting in postsynaptic membrane persistence depolarization (Cook *et al.*, 1990) [15]. Toxic effects of anatoxin-a(s) can be blocked temporarily by atropine because of its direct agonistic characteristics at muscarinic receptors with indirect neuromuscular blocking (Miller *et al.*, 2017) [43].

Saxitoxin

Saxitoxin can be produced in freshwater and marine water both environments. In the freshwaters, saxitoxins are produced by cyanobacteria of Genus Anabaena, Aphanizomenon, *Planktothrix*, *Cylindrospermopsis*, *Lyngbya*, and Scytonema, etc. (Smith *et al.*, 2012; Wiese *et al.*, 2010) [65, 75]. However, saxitoxins have been reported to accumulate in freshwater fish such as tilapia (Galvao *et al.*, 2009) [19]. Saxitoxins are non-volatile, tricyclic, perhydro purine alkaloids (Schantz *et al.*, 1975) [59], which are heat stable in

acidic environments and highly water-soluble (Trevino, 1998) [69]. Their activity is mediated through positively charged guanidium groups (Wiese *et al.*, 2012) [90].

Mode of Action

Saxitoxins are selective, reversible, voltage-gated sodium channel blockers (Huot *et al.*, 1989; Tarnawa *et al.*, 2007; Walker *et al.*, 2013) [30, 67, 74]. This toxic compound is one of the most potent natural toxins that acts on neurons' voltage-gated sodium channels, preventing normal cellular function that leads to paralysis. Opening the voltage-gated sodium channel can occur while changing in voltage or some ligand binds with integral membrane protein in the right way. It is essential for the proper action potential. Without this potential, nerve cells can't transmit signals to a specific region of the body, and its enervation is disconnected from the CNS, resulting in the paralysis of the affected region (Huot *et al.*, 1989) [30]. Saxitoxin binds to the sodium channel reversibly. It binds directly to the pore of the channel protein, obstructing the opening and preventing sodium ions from passing through the blood-brain barrier and sodium channel blockade in the CNS (Borinson and McCarthy, 1977) [9]. As a result, the nervous system shuts down.

As evident from above discussion, it is confirmed that the most of the cyanotoxins produce negative effect on physiology and so obviously it will affect the growth of fish and overall production in aquaculture. The same is being witnessed in intensive aquaculture system on filed when the blooms of the blue green algae appear it leads slow growth, mortality and poor animal production performance.

Potential impact on feed performance

There are enough reports of cyanotoxin toxicity and fish kill in natural water. However, its impact on the cultural system has been very scarcely studied. The algal blooms create many aquaculture issues such as deviated dissolved oxygen and depletion of oxygen at night leading to fish kills in ponds. In addition to it, the dissolved oxygen, some other parameters like PH, and alkalinity fluctuations are prevalent. When such blooms crash, it leads to an increase in total nitrogen and sometimes nitrite levels (as from farm data). The anoxic condition created due to heavy bloom or degradation of scums or sludge after death and decay of the algal is another deleterious issue in aquaculture. So, the overall alteration in water quality in terms of dissolved oxygen decrease, pH, fluctuation, an increase of ammonia and other toxic nitrogen components like nitrite, and obnoxious gases due to decaying of the dead mat of blooms give a sublethal impact. In such sublethal impact, reduced feed performance due to stress and poor feed intake is prevalent in almost all kinds of bloom. However, the toxic bloom of cyanobacteria imposes other threats of damaged histoarchitecture of vital organs and poor physiological efficiency (as per the result of trial in our lab). Therefore, the feed utilization efficiency and overall feed performance efficiency get reduced.

Mitigation strategies

The increased occurrence of toxic blue-green algal blooms affects tremendously potential human health risks and even fish growth and health globally. For the sake of environmental sustainability, sustainable development of aquaculture, and economic vitality, new technology are required in the future to prevent/suppress harmful cyanobacterial blooms (Hudnell, 2008, 2010; Srivastava *et al.*, 2013; Harris *et al.*, 2014) [28, 66, 23]. A group of Taiwanese researchers used solid-phase extraction liquid chromatography-mass spectrometry to accurately identify the presence of microcystins, nodularin, anatoxin-a, and cylindrospermopsin concurrently in various water samples and discovered that it was an appropriate approach for monitoring cyanotoxins (Yen *et al.*, 2011) [81]. There are several factors that contribute to the occurrence of harmful cyanobacterial blooms, such as nutrient input, wind velocity, sediment deposition, reduced water flow, increased salinity and temperature gradients, global warming, and drought. These can be controlled to some extent in order to eliminate or reduce the occurrence of blooms. Bloom suppression methods should be environmentally sustainable and have no negative impact on aquatic ecosystems. To mitigate the harmful cyanobacterial bloom incidences, various mitigation strategies or approaches such as chemical, biological, and research and management approaches could be considered.

Chemical approaches

To a certain extent, some chemicals as algicides can control cyanobloom, but they can also recontamination the water bodies or culture systems (Murray Gulde *et al.*, 2002; Van Hullebusch *et al.*, 2002; Jančula and Maršálek, 2011) [45, 91, 33]. Certain pigments (aquashade) can reduce light availability and inhibit the growth of harmful algae; however, this approach may not be effective due to growth inhibition of other beneficial microalgae, negatively influencing fish growth and aquatic ecosystems. (Dai *et al.*, 2012) [16], recently demonstrated the rapid removal (up to 98.99 percent) of MC-LR by a low-cytotoxic microgel-Fe (III) complex. It was also discovered that peroxidation with chlorine dioxide, followed by flocculation and settling, was effective in removing cyanobacterial blooms and MCs (Bogialli *et al.*, 2013) [13]. The use of aluminum salts, slaked lime [Ca $(OH)_2$] or calcite ($CaCO_3$) (Prepas *et al.*, 2001; Zhang *et al.*, 2001) [86, 86], salt of copper ($CuSO_4.5H_2O$) (Murray-Gulde *et al.* 2002) [45] those are approved by the United States Environmental Protection Agency (USEPA) for the use of removing algal bloom in fish production ponds (Schrader *et al.*, 2004) [58]. Recently, (Jančula and Maršálek, 2011) [33], reviewed the availability of different chemical compounds to prevent and manage cyanobacterial blooms (Table 2).

Biological approaches

For controlling blue-green algae blooms, the biological mechanisms may be one of the eco-friendly and viable methods. In such interventions, nutrient uptake or availability regulation, alterations in normal physiology (such as a decrease in photosynthetic pigment), direct feeding of cyanobacterial biomass by some aquatic organisms (such as gastropod), occurrence and growth of the aquatic plants (such as submerged plant) may be promising methods of ecological restoration (Bond and Lake, 2003; Qin *et al.*, 2006; Zhang *et al.*, 2008; Zhang *et al.*, 2012, 2014) [8, 54, 87, 85] in natural water bodies. But for aquaculture systems, the methods shall be standardized in response to cultured species, and culture practice and should be aquaculture friendly. Some aquatic plants produce allelochemicals that inhibit the growth of cyanobacteria and other phytoplankton (Nakai *et al.*, 2000; Körner and Nicklisch, 2002) [46, 37]. However, for aquaculture, biodegradation of blue-green algae or algal mat using various species/strains of bacteria and other organisms may be the most effective method for controlling the fate of

some cyanotoxins in natural waters (Zhang *et al.*, 2008; Manage *et al.*, 2009; Lawton *et al.*, 2011; Rastogi *et al.*, 2014) [87, 40, 38, 55] (Table 3). The biological control in which fishes can consume directly and the fish's tolerance to its toxicity can be one option which will have management and fish production together.

Research and Management Approaches

The development of a waste water and aquaculture effluents use research and management program have more scope for preventing or controlling the global incidence of algal blooms in aquatic ecosystem and aquaculture systems. While preserving ecological integrity and sustainability, the various environmental factors such as nutrient-enrichment, global climate, feed-based alteration in nutrient composition of water, and change of microbial community contribute to an increase in the occurrence and growth of harmful blue-green blooms. It requires a critical protocol and standard to develop well-defined management strategies (Paerl *et al.*, 2011a, b) [51]. As phosphorus enrichment plays an essential role in the growth of different cyanobacterial microalgae, the same has got more boost due to plant-based protein like soya in aquafeed. So, the phosphate enrichment in the culture system and water bodies and their catchment area is one of the significant factors to be controlled. Its input control into a water reservoir may be an effective management strategy for aquatic ecosystem restoration in the future. Prior to wastewater treatment, modeling of different bodies (Tyler *et al.*, 2009; Coad *et al.*, 2014) [70, 13], may be required to reduce the incidence of cyanobacterial blooms caused by bloom-boosting organic or inorganic nutrients from common aquaculture and agriculture practices such as excessive use of fertilizers (e.g., NPK) and detergents (Conley *et al.*, 2009; Paerl *et al.*, 2011a; Jacquet *et al.*, 2014) [14, 51, 32]. Furthermore, primary research and quantitative ecological awareness of bloom incidence in the aquaculture system and increasing phosphate utilization in aquafeed and reducing fecal or leaching loss in water have to be emphasized. It can be a helpful tool in guiding aquaculture water quality management and controlling the harmful blue-green algal bloom incidence.

Table 1: Cyanotoxins their target organ of toxicity and nature (source: derived from Geoffrey A. Codd, Steven G. Bell and William P. Brooks Department of Biological Sciences, University of Dundee, Dundee DDI 4HN, U.K.)

Name of the toxin	Toxin class/primary target organ of the toxin	Nature of compound
Microcystin	Hepatotoxin Liver Tumor promotion	Cyclic heptapeptide
Nodularin	Hepatotoxin Liver Tumor promotion	Cyclic pentapeptide
Cylindrospermopsin	Hepatotoxin/cytotoxin Liver and kidney	Alkaloid
Anatoxin-a Homoanatoxin-a Anatoxin-a(S)	Neurotoxin Neurons Neurotoxin Neurons	Alkaloid (organophosphate)
Saxitoxins	Neurotoxins Neurons	Alkaloid
Aplysiatoxin	Dermatotoxin Skin Tumor promotion	Alkaloid
Debromoaplysatoxin	Dermatotoxin Skin Tumor	Alkaloid
*Lyngbya*toxin-a	Dermatotoxin Skin	Alkaloid
LPS	Pyrogenic Unspecific health effects such as fever	Call wall component

Table 2: Potential chemicals and compounds for management of the cyanobacteria in aquatic system and culture ponds (Source: Jančula, and Maršálek, 2011)

Allelochemicals	Source	Target Cyanobacteria	EC50	Mechanisms	References
Bacillamide	*Bacillus sp.* (Jeong *et al.* 2003) [92]	*M. aeruginosa, Anabaena circinalis, Anabaenopsis circularis*	29-160 microgram mL^{-1}	Morphological & ultrastructural changes, growth inhibition, reduction and collapse of gas; vesicles, distortion of cell shape.	Churro *et al.*, 2010 [12]
Gallic acid, (+)- catechin, Ellagic acid Gramine	*Myriophyllum spicatum* Higher plant tannin extracts (Robinson, 1967) [93]	*M. aeruginosa*	1.0 mg l^{-1} 5.5 mg l^{-1} 5.1 mg l^{-1} 0.5-2.1 mg l^{-1}	Produced free radicals, growth inhibition Oxidative damage, lipid peroxidation	Hong *et al.*, 2009 [25]
Phenolic compounds (HHDP-di- and –tri-galloyl glucose)	*Myriophyllum spicatum*	*Anabaena variabilis*	-	Growth inhibition	Bauer *et al.*, 2009 [3]
Vanillic acid (VA) Ferulic acid (FA) Caffeic acid (CA) Protocatechuic acid (PA)	*Hydrilla verticillata, Vallisneria spiralis*	*M. aeruginosa*	60 mg l^{-1} 130 mg l^{-1} 5 mg l^{-1} 15 mg l^{-1}	Growth inhibition	Gao *et al.*, 2011 [20]
Nepodin Isoalantolactone Chrysophanol	*Limonium myrianthum* *Inula helenium* *Limonium myrianthum*	*Oscillatoria perornata*	> 100 microgram mL^{-1} 10 microgram mL^{-1}	Growth inhibition	Cantrell *et al.*, 2007 [10]
Tryptamine	Natural/ Synthetic	*M. aeruginosa, Anabaena circinalis, Anabaenopsis circularis*	< 4.15 microgram mL^{-1}	ROS production, lipid peroxidation, irreversible membrane damages	Churro *et al.*, 2010 [12]

Table 3: Some bacterial isolate potentially useful for controlling blue green algal bloom (source: Zhang *et al.*, 2008; Manage *et al.*, 2009; Lawton *et al.*, 2011; Rastogi *et al.*, 2014) [87, 40, 38, 55]

Bacterial Isolates	Strains	Microcystin Variants	Reference
Arthrobacter sp.	C6, F7, F10, R1, R4, R6, R9	LR	Manage *et al.* 2009; Lawton *et al.* 2011 [40, 38,]
Bacillus sp.	AMRI-03, EMB	LR, RR	Hu, *et al.*, 2012 [29]
Sphingomonas sp.	MD- 1	LR, RR, YR	Saito, *et al.*, 2003 [57]

Sphingomonas sp.	7 CY	LR, RR, LY, LW, LF	Ishii, *et al.*, 2004 [31]
Sphingopyxis sp.	LH21	LR, LA	Ho, *et al.*, 2007 [24]
Sphingopyxis sp.	USTB-05	RR, YR	Xu, *et al.*, 2015 [78]
Sphingopyxis sp.	C-1	LR, RR	Okano, *et al.*, 2009 [49]

Conclusion

Cyanobacterial blooms are becoming more of a problem in both wastewater treatment and drinking water systems. The leading causes of cyanoblooms worldwide are eutrophication and global climate change. The production of several freshwater cyanotoxins, including MCs, cylindrospermopsin, anatoxins, saxitoxins, have been identified as major environmental contaminants in nearby aquatic ecosystems. Several mitigation strategies have been tested and implemented in laboratories; however, their efficacy in removing blooms in field environments has not been confirmed. Implementing effective mitigation strategies such as chemical, biological, and public awareness approaches to environmental awareness may be the most realistic nutritional measure to overcome the global incidence of algal blooms and achieve a sustainable environment. Although some natural algicidal compounds are highly effective at controlling cyanoblooms, their production and availability remain extremely limited. The cost-effective synthesis of these biochemicals would be highly beneficial in controlling cyanoblooms.

Furthermore, some cyanobacteria may develop resistance to certain chemicals. The use of biocides or various biological processes against cyanoblooms may have unintended consequences for other aquatic organisms. Furthermore, a combined policy should be strictly regulated to reduce the bloom-boosting cause, such as anthropogenic eutrophication of aquatic ecosystems and aquaculture bodies.

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