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Cyanotoxins uptake and accumulation in crops: Phytotoxicity and implications on human health

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ABSTRACT

The invasive nature of cyanotoxin-producing cyanobacteria and the adverse effects concerning their toxic impacts have gained heightened scientific attention of late. The persistence of cyanotoxins in irrigation water leads to bioaccumulation in plants, the development of phytotoxic effects, and the threat of groundwater contamination. The accumulation of cyanotoxins in plants is caused by several factors leading to severe toxic effects, including reduced plant growth and seed germination, enhanced oxidative stress, lowered rate of mineral uptake, decreased photosynthetic efficiency, and loss of chlorophyll content. The uptake and accumulation of cyanotoxins in plants can be concentration-dependent, as reported in a myriad of studies. Even though several studies have reported phytotoxic effects of cyanotoxin contamination, field-related studies reporting phytotoxic effects are particularly inadequate. Paradoxically, at realistic conditions, some plants are reported to be tolerant of cyanotoxins. Furthermore, the breadth of adverse impacts of cyanotoxins on human health is significant. Cyanotoxins cause major health effects including cancer, oxidative stress, organelle dysfunction, DNA damage, and enzyme inhibition. This review intends to present compelling arguments on microcystins (MCs), cylindrospermopsins (CYN), β-N-methylamino-L-alanine (BMAA), and anatoxin-a (ANTX-a), their uptake and accumulation in crop plants, phytotoxic effects on plants, and potential health implications to humans. The accumulation of cvanotoxins implants cultivated as food crops, resulting in phytotoxic effects and adverse impacts on human health are serious issues that require scientific inputs to be addressed.

1. Introduction

Cyanobacteria, a fusion of cyan (blue) and bacteria (a prokaryotic organism), constitutes both positive and negative impaction humans (Buratti et al., 2017). Being photosynthetic, cyanobacteria play an important role as primary producers (Machado et al., 2017; Bitten-court-Oliveira et al., 2014). Favourable environmental conditions combined with nutrient availability help the proliferation of cyanobacteria and the formation of cyanobacterial blooms. These blooms can cause severe environmental and health effects (Pelaez et al., 2010). Artificially or naturally-induced water eutrophication and climatic changes are identified as primary reasons for the occurrence and flourishing of cyanobacterial blooms (Machado et al., 2017). Certain

cyanobacterial isolates belonging to specific cyanobacterial species can produce a highly toxic range of secondary metabolites known as cyanotoxins (Table 1). The true purpose of toxins still baffles the scientific community (Cirés et al., 2017; Zanchett and Oliveira-Filho, 2013).

Recent studies on cyanotoxins have highlighted the importance of understanding their presence in agricultural lands since a significant fraction of global freshwater is potentially contaminated and utilized for agricultural practices (Lee et al., 2021). The primary portal of releasing cyanotoxins to the soil is using water contaminated with cyanotoxins or cyanotoxin-producing cyanobacteria for agricultural purposes as a fertilizer (Bouaïcha and Corbel, 2016; Corbel et al., 2014a, 2014b; Machado et al., 2017; Mohamed et al., 2022). The persistence of cyanotoxins in agricultural lands can lead to severe concerns due to their

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relative stability (Corbel et al., 2014a, 2014b; Klitzke et al., 2010). This can lead to adverse effects on crop yield and quality of the product and the accumulation of cyanotoxins along food chains. Similarly, crops irrigated with contaminated water can accumulate cyanotoxins in crop plants at potentially harmful levels for humans (Lee et al., 2017, 2021).

Organic fertilizers containing cyanobacterial biomass enhance soil fertility and crop yield. These also can act as a natural biocide due to cyanotoxins production (Bouaïcha and Corbel, 2016). Equally, the direct application of organic fertilizers containing cyanobacterial biomass (Cao et al., 2018b; Chen et al., 2012a, 2012b) can lead to soil contaminations by cyanotoxins.

Agricultural environments facilitate the successful colonization of cyanobacteria. Certain potential cyanotoxin producers thrive in these soils and release hazardous cyanotoxins. Crops that have been grown in these soils could uptake the cyanotoxins, ending with adverse effects on crop yield and quality (Lee et al., 2021).

Two factors further enhance the bioavailability of cyanotoxins in the soil. The introduction of cyanotoxins into agricultural lands via cyanotoxin contaminated irrigation water (Cao et al., 2018a, 2018b, 2018c; Bittencourt-Oliveira et al., 2016; Drobac et al., 2017; Lee et al., 2017) and the fewer adsorption of cyanotoxins onto the soil. Several studies have reported the uptake of cyanotoxins via the plant root and the existence of these toxins in shoots and leaves (Bouaïcha and Corbel, 2016; Campos et al., 2021; Levizou et al., 2020; Nowruzi et al., 2021). Accumulation of cyanotoxins in plants can lead to phytotoxicity through different mechanisms. These include enhanced oxidative stress, inhibition of seed germination and seedling growth and development, inhibition of the activity of plant regulatory enzymes, damaging plant tissues, and eventually perishing of the plants (Machado et al., 2017; Purkayastha et al., 2010). The earliest records on the phytotoxic effect of cyanotoxins on plants were first recorded on aquatic photoautotrophic organisms including algae and macrophytes (Ikawa et al., 2001; Mitrovic et al., 2004). Recently, significant attention has been focused on the effects of cyanotoxins on terrestrial plants. The bio-accumulation of cyanotoxins in edible plants creates an indirect entry route of these toxins to humans, creating serious health concerns (Sagrane and Oudra, 2009). The primary human exposure routes of cyanotoxins are the consumption of contaminated water; consumption of cyanotoxin contaminated edible plant parts and/or aquatic organisms like fish; direct dermal contact of cyanotoxins during recreational activities and

the intravenous entry of cyanotoxins in medical treatments like dialysis (Drobac et al., 2013; Svirčev et al., 2017). Cyanotoxin exposure and uptake in humans can lead to serious health issues (Kubickova et al., 2019; Buratti et al., 2017). Cyanotoxins are suspected as one of the risk factors for Chronic Kidney Disease of unknown etiology (CKDu), a non-reversible disease condition, mostly recorded from countries involved in agriculture (Manage, 2019).

Scientific studies on the ecology and fate of cyanotoxins in temperate freshwater environments are abundant, whereas limited studies have been reported from humid tropics (Corbel et al., 2014a, 2014b; Magana Arachchi and Liyanage, 2012; Magana-Arachchi et al., 2011). At the same time, researchers have focused their attention on phytoavailability and plant uptake of cyanotoxins (Machado et al., 2017; Bouaïcha and Corbel, 2016). However, a gap is created with the inadequacy of a detailed review on plant uptake pathway mechanisms, phytotoxicity, and human health hazards. Therefore, this review focuses on the cyanotoxin producers, types of specific cyanotoxins, uptake, and accumulation of cyanotoxins in plants, phytotoxic effects of cyanotoxins, and the potential health hazards that are relayed through food chains and exposure to humans. To achieve the successful outcome of this review, reference papers were collected using online databases like Scopus, ScienceDirect, PubMed and Web of Science and the journal articles were carefully read and analysed. The reference papers were collected using main keywords like phytotoxic effects of cyanotoxins, health hazards created by cyanotoxins, cyanotoxin persistence and the published years considered for the reference papers were mainly between 2010 and 2021. More than 500 references were searched, and over 160 articles were used as references in the final manuscript.

2. Emergence and persistence of cyanotoxins in soil

Cyanotoxins are commonly reported in surface waters worldwide, with the highest hepatotoxic microcystins (MCs) production in 50–75% cyanobacterial blooms (Corbel et al., 2014a, 2014b). The occurrence and persistence of cyanotoxins are not limited to freshwater ecosystems (Table 2). However, the highest cyanotoxin levels are reported from algal blooms and scums in freshwater ecosystems (Benayache et al., 2019). Cyanotoxins can enter into soil ecosystems using diverse routes. The major source is the use of cyanotoxin-contaminated untreated water for irrigation (Bouaïcha and Corbel, 2016). When cyanotoxins become

Table 1

Types of cyanotoxins based on chemical structure and the potential producers.

Chemical structure	Cyanotoxin	Toxicity	Some producing genera	Reference
Cyclic peptides	Microcystins	Hepatotoxicity	Microcystis	Bouhaddada et al. (2016)
	-		Dolichospermum	Brutemark et al. (2015)
			Nostoc	Kurmayer (2011)
			Radiocystis	Pereira et al. (2012)
			Fischerella	(Cirés et al., 2014; Fiore et al., 2009)
			Anabaenopsis	(Mohamed and Al Shehri, 2009a)
			Gloeotrichia	Carey et al. (2012)
	Nodularins	Hepatotoxicity	Nodularia	Lundgren et al. (2012)
			Nostoc	(Jokela et al., 2017; Gehringer et al.,
				2012)
Alkaloids	Cylindrospermopsins	Cytotoxicity, Hepatotoxicity,	Cylindrospermopsis	(Hawkins et al., 1997)
		Nephrotoxicity	Aphanizomenon	Wormer et al. (2008)
			Chrysosporum, Dolichospermum	Akcaalan et al. (2014)
			Lyngbya	McGregor and Sendall (2014)
	Saxitoxins	Neurotoxicity	Cylindrospermopsis, Geitlerinema,	Borges et al. (2015)
			Cylindrospermum,	
			Lyngbya	Foss et al. (2012)
	Anatoxin-a	Neurotoxicity	Microcoleus	Wood et al. (2018)
	Anatoxin-a(s)	Neurotoxicity	Anabaena	Pearson et al. (2016)
Lipopeptides	Majusculamides	Cytotoxicity	Moorea	Caro-Diaz et al. (2019)
	Hectochlorins	Cytotoxicity	Lyngbya	Ramaswamy et al. (2007)
	Curacins	Cytotoxicity	Caldora, Lyngbya	(Du et al., 2019; Zhang et al., 2017)
Nonprotein amino	β-N-methylamino-l-	Neurotoxicity	All cyanobacterial genera	Cox et al. (2005)
acids	alanine			
Lipoglycans	Lipopolysaccharides	Endotoxicity	All cyanobacterial genera	Jan-Chrstoph and Elke (2015)

Table 2

The occurrence of cyanotoxins in soil and aquatic ecosystems around the world.

Country/ Region	Soil ecosystem/ aquatic ecosystem	Type of cyanotoxin	Toxin concentration (μg/g in dry weight)	Reference
Quebec, Canada	Silt loam soil from an agricultural field	ANTX-a MC-LR	0.0118 0.0133	Zhang et al. (2020)
Qatar	Hot desert	ANTX-as MCs	0.001 0.001–0.05	Metcalf et al. (2012)
Versailles, France	Silty, sand agricultural soil	MC-LR	$\begin{array}{c} 1.6 \times 10^{-3} - \\ 3.9 \times 10^{-3} \end{array}$	Corbel et al. (2016)
South Africa	Nhanganzwane Dam	MCs	23,718	Oberholster et al. (2009)
Svalbard, Norway	Polar desert	ANTX-a	0.3–0.6	Chrapusta et al. (2015)
Australia	Cobaki Lake	CYN	101.4	Everson et al. (2011)
China	Lake Taihu	MCs	34.2	Liu et al. (2011)
Kenya	Lake Baringo	ANTX-a	0.05–0.21	Ballot et al. (2003)
Spain	River Segura	ANTX-a	1.6	Aboal and Puig (2005)
Turkey	Lake Kovada	MC-LR	0.73–48.5	Gurbuz et al. (2009)

persistent in soil, it increases their bioavailability to plants and the tendency for groundwater contamination.

The release of large quantities of untreated cyanobacterial biomass from contaminated water bodies to forest ecosystems is another method of cyanotoxin introduction to soil-based ecosystems (Chen et al., 2012a, 2012b). Earlier, cyanobacteria were well known as a potential biofertilizer in paddy cultivation. It allows nitrogen fixation in the soil, supplying nitrogen, essential for plant growth (Mishra and Pabbi, 2004). Even though these cyanobacterial fertilizers are used to enhance soil fertility and crop yield, the production, and accumulation of cyanotoxins such as MC-LR are lethal to the root system of rice plants. The toxicity impact the root morphogenesis and the development of adventitious roots (Chen et al., 2012a, 2012b). Furthermore, using cyanobacterial fertilizers in the rainy season can lead to a higher level of persistence of cyanotoxins like MC-LR, which could leach through the soil and create further harmful groundwater contaminations. This effect is more pronounced in clay-rich soil reported with a higher cyanotoxin persistence (Chen et al., 2006).

Though reports on cyanotoxin persistence in the soil are scarce, it is suggested that soils abundant with clay and organic matter have high adsorption of cyanotoxins (Zhang et al., 2021). Miller et al. (2001) report from a study conducted in South Australia that clay and high organic carbon-containing soil possess a higher toxin adsorption coefficient. Therefore, such soils could be utilized as an effective agent in removing cyanotoxins. This is further supported by the studies conducted by Miller and Fallowfield (2001), which report the highest cyanotoxin removal efficiency of soils containing high organic and clay over sandy textured. Furthermore, as presented in Järvenpää et al. (2007), the adsorption of MCs by soil reduces the bioavailability of MCs for plant absorption. The degree of adsorption depends on the soil characters where sandy soilis poor at adsorbing cyanotoxins. The chemical binding supports the persistence of cyanotoxins in the soil with charged particles in the ground rather than physical adsorption. As shown by Chen et al. (2006), the retention of MCs in the soil is enhanced by the chemical bonding between the metal ions in the soil and the oxygen and nitrogen atoms in the chemical structure of MCs.

Similarly, the binding strength of cyanotoxin to the soil is affected by the pH of the medium (Zhang et al., 2020). Furthermore, reduced adsorption of cyanotoxins to the soil enhances the bioavailability of these toxins to plants. Hence, it is vital to learn about the persistence of cyanotoxins in the soil ecosystem in the dissolved form and as cvanobacterial cells. This could be taken as a direct or an indirect measure in determining the magnitude of phytotoxicity. The stability of cyanotoxin in a soil ecosystem depends on the degradation efficiency created by different cyanotoxin degradation methods; photolysis, hydrolysis, and bacterial degradation (Buratti et al., 2017; Corbel et al., 2014a, 2014b). Cyanotoxins could be degraded by UV exposure (Chintalapati and Mohseni, 2020) and by the activity of cyanotoxin degrading bacteria (Dziga et al., 2016). Under natural conditions cylindrospermopsins (CYN) have a high persistence over MCs due to their lower photodegradation rate (Bouaïcha and Corbel, 2016). Therefore, the degree of degradation depends on the chemistry of cyanotoxin and their tolerance level towards a particular degradation method. Chen et al. (2006) and Miller and Fallowfield (2001) reported that the direct utilization of active cyanobacterial cells as natural antagonists in removing cyanotoxins should be done with extra care since specific soil properties can facilitate the strong persistence of cyanotoxins.

Furthermore, the adsorption of cyanotoxins such as MCs on sediments and soil particles negatively affects the photochemical degradation of cyanotoxins (Thirumavalavan et al., 2012). Chen et al. (2006), reported the persistence of MCs in agricultural soils in 6–17.8 days. Similarly, Metcalf et al. (2012) report the detection of MCs in a herbarium specimen of cyanobacteria after 170 years. Accordingly, the persistence of cyanotoxins in dead and dried cyanobacterial cells for an extended period imposes the risk of re-immersing them back to the soil via irrigation waters. Due to a poverty in studies related to the cyanotoxin persistence in the soil, it is hard to provide an exact landscape to remove toxins from soil ecosystems altogether. Further studies associated with natural ecosystems will help the formation of opinions on the types and periods of cyanotoxin persistence and removal strategies.

3. Uptake and accumulation of cyanotoxins in plants

3.1. Microcystins (MCs)

The mechanisms of cyanotoxin uptake in plants are relatively poorly studied in both field and laboratory conditions. However, it is predicted that the membrane permeability towards MCs is based on polarity (Machado et al., 2017). Therefore, the process of crossing plant cell membranes by microcystins could include root absorption or simply diffusion (Machado et al., 2017; Corbel et al., 2014a, 2014b). MCs are polar molecules although possessing hydrophobic groups. Therefore, it is suggested that the uptake of such MC into the cells requires specific membrane transporters (Llana-ruiz-cabello et al., 2019). Despite the paucity of information in relation to plants MCs uptake mechanisms, several studies report MCs uptake from plant roots and the appearance of such toxins in different plant parts, including shoots and leaves (Corbel et al., 2016; Gutiérrez-Praena et al., 2014) (Table 3). Tegeder and Rentsch (2010) report the presence of several plant membrane transporters such as LHT (lysine/histidine) transporter, OEP plastid outer envelope protein, PTR-1 like peptide transporter, and OPT oligopeptide transporter that have different affinities towards peptides and amino acids which could assist in cyanotoxin uptake into plants.

The exposure of plant organs to spray irrigation of cyanotoxincontaminated water could lead to cyanotoxin absorption into the plant (Hu et al., 2016). Furthermore, MCs being peptides, it is reasonable to hypothesize that these amino acid and peptide transporters might favour the uptake of MCs to plants. As reported in Pflugmacher et al. (2019), MC-LR detected in the guttation drops and xylem sap of *Triticum aestivum* seedlings exposed to 100 mg L⁻¹ of MC-LR providing evidence for the translocation of MC-LR within the plant. Furthermore, the same study reported MC-LR detection in roots, stems, and leaves of *T. aestivum* seedlings, providing evidence for the uptake and translocation of MC-LR through spray irrigation. Similarly, the translocation of MCs into edible plant seeds such as rice is also reported (Manage, 2019; Chen et al., 2012a, 2012b). The high water absorption of rice plants (Chen et al., 2012a, 2012b) results in an extensive accumulation of MCs in shoots,

Table 3

Cyanotoxin uptake by agricultural plants u.

Plant	Common name	Plant part detected with cyanotoxins	Type of cyanotoxin	Exposure concentrations	Period of exposure (days)	Cyanotoxin concentration (µg/kg) in plant tissue	Reference
					(and the state of t
Lactuca sativa	Lettuce	leaves	MC-LR	0.5 μg/L, 2.0 μg/L, 5.0 μg/L and 10.0 μg/ L	15	$32.99 \pm 5.23 - 143.35 \pm 12.19$	Bittencourt-Oliveira et al. (2016)
			MC –RR	– 0.15 µg/L, 0.5 µg/L, 1 µg/L, 3.0 µg/L	15	$\begin{array}{c} \textbf{6.32} \pm \textbf{0.13} \textbf{-} \textbf{15.00} \pm \\ \textbf{1.78} \end{array}$	
Phaseolus vulgaris	Bean	pods	MC	132 µg/L	-	0.125–0.391 μg kg ⁻¹	Mohamed et al. (2022)
Oryza sativa	Rice	rice grain	MC -LR	-	A field sample	0.04–3.19	Chen et al. (2012a, 2012b)
Triticum aestivum	Wheat	root	β-Ν-	1000 µg/L	14	57 ± 19	Contardo-Jara et al.
		shoot	methylamino-L- alanine		28	100 ± 15	(2014)
Spinacia oleracea	Spinach	leaves	CYN	50 μg/L	21	36.97 ± 10.25	(Llana-ruiz-cabello et al.,
			MC		21	Below the detection limit	2019)
		root	CYN	10 μg/L, 50 μg/L	21	Not detected	
			MC		21		
Lactuca sativa	Lettuce	leaves	CYN	50 μg/L	21	9.4 ± 2.38	
			MC		21	Not detected	
		roots	CYN	10 μg/L, 50 μg/L	21		
			MC		21		
Allium fistulosum	Onion	root	β-Ν-	4.5 μg/L	60	~3000	Esterhuizen-Londt and
		shoot	methylamino-L-		60	~ 500	Pflugmacher (2019)
Lactuca sativa	Lettuce	root	alanine		60	~390	
		shoot			60	Not detected	
Pisum sativum	Pea	shoot	MC -LR	-	1	64.8	Peuthert et al. (2007)
		root			1	90.6	
Ipomoea aquatica	Water spinach	edible plant tissues	MC -LR	180 µg/L	120	350.82 ± 2.86	(Manage, 2019)
Oryza sativa (Cultivar - Suwandel)	Rice	rice grain			120	$\textbf{429.83} \pm \textbf{4.39}$	
Brassica rapa subsp.	Chinese	root	β-Ν-	$1.8-16.3 \ \mu g \ m L^{-1}$	10	2320	Li et al. (2019)
Pekinensis	cabbage	shoot	methylamino-L-		06	2010	
		leaves	alanine		15	1670	
Solanum	Tomato	shoot	MC -LR	2300 μg/L	2	$30.4 imes 10^3$	Corbel et al. (2016)
lycopersicum		fruit			2	Not detected	
(Cultivar -		root			2	$311.8 imes 10^3$	
MicroTom)		leaves			2	$103.5 imes 10^3$	
Capsicum annuum	Bell pepper	fruit	MC -LR	245 μg/L	90	118	Drobac et al. (2017)
		leaves			90	Not detected	
Brassica oleracea var. italica	Broccoli	root	MC -LR	10 μg/L	20	0.9–2.4	Järvenpää et al. (2007)
Sinapis alba	White mustard				19	2.4–2.6	
Brassica juncea	Brown mustard	leaves	CYN	18–35 μg/L	30	$\textbf{4.29} \pm \textbf{1.48}$	Kittler et al. (2012)
Cucumis sativus L.	Cucumber	fruit	MC	1000 μg/L	7	29.64	Zhu et al. (2018a, 2018b)
Raphanus sativus	Radish	leaves roots	MC	_	A field sample	~225 ~360	Mohamed and Al Shehri (2009b)

stems, and roots in long-term exposure to MC-contaminated irrigation water (Cao et al., 2018a, 2018b, 2018c). Chen et al. (2012a, 2012b) report the accumulation of MC-LR in 21 out of 44 studied samples of *Oryza sativa*. The same study does not notify MC-LR accumulation in rice grains above the WHO recommended daily intake for humans, 0.04 μ g kg⁻¹ d⁻¹ (World Health Organisation, 2017). However, a similar level of accumulation in rice grains in a country like Sri Lanka, where rice is consumed for all the main meals, the consequences could be far more lethal.

The uptake and accumulation of cyanotoxins into edible plant parts could further lead to their absorption in higher levels of food chains and severe health hazards (Redouane et al., 2019; Corbel et al., 2014a, 2014b). Several studies have reported excessive MC concentrations in edible plant parts compared to the WHO recommended daily intake of 0.04 μ g kg⁻¹ d⁻¹ (Drobac et al., 2017; Lee et al., 2017; Bittencourt-O-liveira et al., 2016). However, experiments based on realistic environmental conditions are adequately required in making exact conclusions relating to phytotoxicity. The degree of MC accumulation in plants is dependent upon several factors. These include the species or the

cultivar, type of plant organ exposed to the toxin, the developmental stage of the plant, and the duration of exposure (Lee et al., 2017; Pindihama and Gitari, 2017; Redouane et al., 2019; Zhang et al., 2021). According to the literature, the accumulation of MCs in the plant root is much more extensive when compared to other plant organs (Chen et al., 2012a, 2012b; Romero-Oliva et al., 2014). Concerning human health, edible plant roots like carrots accumulate a significant level of MCs (Lee et al., 2017). Furthermore, in a meta-analysis of MCs in 35 plant species, conducted by Zhang et al. (2021) a team of scientists came to a conclusion that prominent phytotoxic effects in MC contamination are reported in wheat, white mustard, corn and garden cress. Similarly, the same study reports that the bioaccumulation of MCs in the edible parts of leafy vegetables like parsley and cabbage is three times more intensive than other agricultural plants. Similarly, a study conducted by Mohamed and Al Shehri, (2009a, 2009b), has recorded the potential of groundwater in creating MC contaminations in agricultural plants. Vegetable plants collected from agricultural land utilizing MC contaminated groundwater have been documented to accumulate significant concentrations of MCs in leaves and roots. This is relatively an

unexplored area related to MC contaminations, even though it could lead to unintentional but severe MCs accumulations. Nevertheless, a majority of MCaccumulated root systems are not consumed by humans as a source of food (Table 3).

The effect of the plant developmental stage in MC accumulation is also documented in certain studies. Levizou et al. (2017) found that lettuce seedlings accumulate high levels of MCs compared with mature leaves at the second and fourth leaves stages. The assessment of mature plants harvested at marketable volumes for MC accumulation showed a 2.4-factor increase in the MC concentration compared to the WHO recommended daily intake of 0.04 μ g kg⁻¹ d⁻¹. This finding is further supported by observing a high MC concentration in cucumber roots at the seedling stage than in the flowering and fruiting stages (Zhu et al., 2018a, 2018b). It is evident that the early stages of plant development are more vulnerable to MC accumulation, but this requires further confirmation with more specific studies among different plant species.

Studies have shown that the exposure time of MC directly affects its accumulation in plant organs (Zhu et al., 2018a, 2018b; Drobac et al., 2017; Cordeiro-Araújo et al., 2016). This fact could be further supported by comparing the studies conducted by Gutiérrez-Praena et al. (2014) and Corbel et al. (2016), based on tomatoes. The 90 days of exposure to MCs by daily irrigation in Corbel et al. (2016), has reported the accumulation of MC-LR only in leaves and roots of tomato plants but not in fruits. However, Gutiérrez-Praena et al. (2014) reported accumulation of MC-LR in leaves, roots, and fruits of tomato plants. Intriguingly, Gutiérrez-Praena et al. (2014), explained that MC-LR detection in tomato fruits was evident in the first week of exposure, and the values dropped below the detectable levels in the second week. Therefore, it is not a case of extended exposure times; however, lower exposure periods can also lead to drastic outcomes concerning phytotoxicity and human health. Still the accumulation of MCs in plants is not necessarily time-dependent. Individual understanding of the effect, activity, uptake, and accumulation of MCs in different edible plants will help to overcome adverse health impacts due to the consumption of MC contaminated food. Furthermore, high exposure concentrations and extended exposure time make the depuration process of MC more challenging and less efficient (Cordeiro-Araújo et al., 2016). Experiments based on realistic environmental conditions are further recommended and encouraged to make precise conclusions on the phytotoxic effects at actual field conditions.

3.2. Cylindrospermopsins (CYN)

Like MCs, the CYN uptake and accumulation in plants have not been studied extensively. Owing to the recurrent identification of CYN as a potential contaminant in irrigation systems and croplands, studying its uptake and accumulation in plants is a timely exercise The extensive extracellular availability due to the water solubility, stability under a diverse range of conditions, capability of forming covalent bonds with DNA and RNA, and the inhibitory effect on protein synthesis, CYN could lead to distinct phytotoxic and health effects different to those reported from MCs (Guzmán-Guillén et al., 2017). Similar to MCs, studies on CYN uptake mechanisms are also infrequent. CYN-based studies concerning terrestrial plants are rare compared to aquatic plants (Machado et al., 2017). However, the uptake and accumulation of CYN in several plants are summarized in Table 3. The accumulation of CYN in edible plants shows a concentration-dependent pattern (Kittler et al., 2012). The plant leaves were reported to be contaminated with one-fifth of CYN concentration as found in an irrigation water sample which points to a significant level of CYN uptake in terrestrial plants. Similarly, the same study provides evidence for the root-to-leaf transport of CYN in Brassica vegetables. However, the importance of experiments related to environmentally relevant concentrations concerning the CYN uptake is highlighted.

Conversely, White et al. (2005) report the absence of CYN in the leaves, shoots, or roots in a submerged aquatic plant, *Hydrilla verticillata*,

as CYN was not uptaken by the plant cells. Instead, CYN was observed to be adsorbed to the cell wall. The studies conducted by Kittler et al. (2012) were done in a soil-free system ignoring the effect of CYN adsorption into the soil. Nevertheless, Pereira et al. (2017), a study conducted in soil, reports the absence of CYN in the edible plant tissues, leaves, and stems of parsley and coriander after ten days of CYN exposure, which could be due to the adsorption of CYN into soil particles. Therefore, it is evident that the soil adsorption of CYN is critical concerning the CYN bioaccumulation in plants.

CYN is abundantly found in the environment in its dissolved form than within the cyanobacterial cell (Machado et al., 2017). Therefore, the possible route for CYN absorption to the plant is transdermal absorption. At the same time, the vascular system is the relevant route of CYN transport within the plants, which leads to the accumulation of CYN in other plant organs addition to roots (Llana-ruiz-cabello et al., 2019). As reported by Prieto et al. (2011), the roots reported 15 μ g/g of CYN, and the leaves reported a slightly lower 12.5 μ g/g of CYN, which states that roots show a significant accumulation of CYN compared to leaves.

The CYN uptake and accumulation in plants are governed by selective factors such as the CYN concentration, the type of the plant part exposed to CYN, and the exposure time. The importance of these factors is demonstrated in studies conducted by Llana-ruiz-cabello et al. (2019) using *Spinacia oleracea* (Spinach) and *Lactuca sativa* (Lettuce). CYN accumulation in lettuce roots was higher than in leaves. Conversely, in spinach, the highest accumulation of CYN was observed in leaves. CYN accumulation in both plants was observed to increase with increasing the exposure concentration for 21 days, as explained in the study by Llana-ruiz-cabello et al. (2019).

In contrast, Flores-rojas et al. (2019) reported a decrease in CYN accumulation in *Lemna minor* (duckweed) after the first 24 h of CYN exposure. Therefore, designing studies identifying CYN accumulation based on environmentally realistic conditions will contribute to developing management strategies in controlling adverse effects related to CYN.

3.3. β -N-methylamino-L-alanine (BMAA) and anatoxin-a (ANTX-a)

β-N-methylamino-L-alanine (BMAA) is a potential neurogenerative disease agent (Han et al., 2020). The accumulation of cyanotoxins in plants other than MCs and CYN is minimally studied, and their uptake mechanisms are unknown. However, rarely occurring cyanotoxins can even impose harmful phytotoxic effects and human health hazards similar to MCs and CYN even though they are not detected recurrently. The uptake of BMAA was reported in several crops, including Medicago sativa (Samardzic et al., 2021), Triticum aestivum (Contardo-Jara et al., 2014), Chinese cabbage (Li et al., 2019), Lactuca sativa, and Allium fistulosum (Esterhuizen-Londt and Pflugmacher, 2019) (Table 3). When comparing the studies conducted by Contardo-Jara et al. (2014) using T. aestivum and the study by Li et al. (2019) using Chinese cabbage, it is clear that uptake and accumulation of BMAA in Chinese cabbage is significantly higher than that of T. aestivum. This study provides evidence for the effect of the plant species exposed to BMAA in its accumulation within the plant. Furthermore, plant organs in Chinese cabbage had more protein-associated BMAA than the freely available form. The highest concentration $(13.82 \,\mu g/g)$ of BMAA was reported in leaves, which is the edible part of the plant. Esterhuizen-Londt and Pflugmacher (2019) reported that BMAA was not detected in crop plants cultivated using BMAA contaminated irrigation water, which provides divergence concerning the primary method of cyanotoxin entry to agricultural lands.

Even though the uptake mechanism of BMAA into plants is minimally studied, its structure and chemical composition assist in postulating potential uptake mechanisms and bioaccumulation in plants. BMAA is a non-lipophilic and non-protein amino acid that is hydrophilic and exhibits highly polar characteristics (Contardo-Jara et al., 2018; Han et al., 2020). Concerning the polar nature of BMAA, the vascular system could be suggested as a potential uptake pathway of BMAA into plants. Similarly, the non-lipophilic properties of BMAA further manifest the inability of BMAA to enter plant systems through fat-soluble pathways. Overall, the transformation and bioaccumulation of BMAA within plant cells should be extensively studied concerning diverse aspects. However, concerning the chemical properties, the bioaccumulation pathway of BMAA into plant cells could be assisted by water dissolved routes. Furthermore, the phospholipid bilayer of the plasma membrane could be expected to act as a barrier for bioaccumulation into plant cells owing to the non-lipophilic nature of BMAA (Esterhuizen-Londt and Pflugmacher, 2019; Samardzic et al., 2021).

Plant-related studies concerning anatoxin-a (ANTX-a) are only a handful. Ha et al. (2014) explained that the aquatic plant *Ceratophyllum demersum* actively uptake ANTX-a and other cyanotoxins in the initial 24 h of exposure. The further uptake is reduced due to the metabolization and the elimination of the toxin, which is similar to the conditions reported about CYN uptake in duckweed (Flores-rojas et al., 2019). Furthermore, the same study reports the concentration-dependent uptake of ANTX-aby *C. demersum*. A linear correlation was shown with the increase in the exposure concentration of ANTX-a (Ha et al., 2014). These observations presume the tangibility to utilize certain aquatic plants as potential removal agents of cyanotoxins. Such technologies need to be further investigated using natural conditions and using aquatic plants belonging to different genera.

Studies concerning the uptake pathway and bioaccumulation of ANTX-a in plants are highly rare. However, similar to BMAA, plant uptake of ANTX-acould be speculated using its chemical structure and properties. ANTX-ais a bicyclic secondary amine, an extremely water-soluble alkaloid with highly polar characteristics (Al-Sammak et al., 2014; Harris, 2017). The extensive water solubility and the polar characteristics of ANTX-a support the prediction of water-supported uptake and transmission with implants. Similarly, as described above in Ha et al. (2014), with the active uptake of ANTX-a and other cyanotoxins in *C. demersum* it could be predicted that the uptake of ANTX-a is supported by the uptake of other cyanotoxins like MCs or CYN. The water-soluble nature of ANTX-acould equally support the bioaccumulation of ANTX-a with in plant cells. Furthermore, this could further assist the successful storage of ANTX-ain the cell sap within the plant vacuole.

Saxitoxin is another commonly occurring cyanotoxin in fresh water cyanobacteria and marine dinoflagellates. Saxitoxins are associated with the modification of cellular osmotic pressure in plants by controlling the opening and closing rhythm of Ca^{2+} , K^+ , and Na^+ ion channels in plant cells (Christensen and Khan, 2020). However, the toxic effects of saxitoxins are minimally studied concerning plants (Bouaïcha and Corbel, 2016; Christensen and Khan, 2020). A recent study conducted by Janiele et al. (2021) using *Lettuce sativa* and *Coriandrum sativum* reports that the toxic level of saxitoxins is more prominent in comparison to microcystins. Similarly, in comparison to *C. sativum, L. sativa* is reported to be more sensitive towards the toxicity created by saxitoxins. Saxitoxin treatment resulted in poor germination and growth, and DNA damage in *L. sativa* plants. However, further experimental data is required in governing the activity and persistence of saxitoxins in plants.

4. Phytotoxic effects of cyanotoxins in plants

The knowledge concerning the activity and toxicity of cyanotoxins in terrestrial organisms is relatively remote compared to aquatic counterparts. As mentioned previously, cyanotoxin contaminated irrigation water constitutes a severe threat of cyanotoxin accumulation in edible plants. Furthermore, cyanotoxin contaminations in food crops account for an indirect route of cyanotoxin entry into animals, including humans (Corbel et al., 2014a, 2014b). Therefore, the transfer of cyanotoxins into human food chains ultimately leads to serious human health hazards. The first record for a phytotoxic effect from cyanotoxins was reported by Kós et al. (1995) due to the inhibition of seedling growth in mustard by

MCs. Since then, with evidence on increased morphological and physiological alterations in terrestrial plants due to cyanotoxin exposure (Fig. 1), researchers interests in the phytotoxic effects of cyanotoxins have gained widespread attention. In this section, the possible phytotoxic effects of cyanotoxins will be discussed.

4.1. Effects on plant growth and development

MCs and CYNs exhibit adverse effects on the growth and development of plants (Levizou et al., 2017). However, most published research on the impact of cyanotoxins in plant growth and development is based on planned laboratory experiments rather than actual field trials. Many of these studies focus on plant roots and leaves (Table 4). As reviewed in Machado et al. (2017), the plant growth effects created by cyanotoxins are influenced by several factors. However, in laboratory-designed experiments using crude or purified extracts, the degree of phytotoxicity and the extent of the morphological or histological alterations tend to vary (Saqrane and Oudra, 2009).

The impact of cyanotoxins on the specialization of plant cells and tissues is minimally studied. However, a study by Pappas et al. (2020) presents the alterations observed in a laboratory-designed research. According to findings, filamentous actin in the cytoskeleton of differentiated and meristematic root cells in Oryza sativa treated with pure MC-LR and a crude extract of MC-LR producing Microcystis flos-aquae extract expressed time-dependent alterations. The changes observed included disorientation and formation of ring-like structures, collapsing of the filamentous actin network in the cytoskeleton upon extensive treatment, inhibition in the cell cycle progression coupled with abnormal condensation in chromatins, and altered structural features in the endoplasmic reticulum and the Golgi apparatus. This evidence, confirms that cyanotoxins' activity could lead to drastic effects at cellular levels in terms of phytotoxicity. In a study conducted by Zhu et al. (2018a, 2018b), it was reported that enhanced growth inhibition was predominantly observed in the seedling stage, and vegetative growth was more susceptible than reproductive events. Similar results were observed by Freitas et al. (2015) where mature plant stages of Lactuca sativa were able to tolerate lower concentrations of MCs and CYN (1 $\mu g/L),$ however high concentrations (10 $\mu g/L)$ were not tolerated. Chen et al. (2012a, 2012b) observed a significant reduction in the root development in rice plants when exposed to an MC concentration between 0.5 and 4 mg mL-1 but was not affected at an MC concentration of 0.01–0.2 mg mL⁻¹. Similarly, in a study conducted to test the effect of MCs in Solanum lycopersicum, Triticum aestivum, and L. sativa, the growth of the primary roots was enhanced at low MC concentrations. Furthermore, high MC concentrations showed growth retardation in S. lycopersicum and L. sativa, but not in T. aestivum (Corbel et al., 2015). Therefore, the predetermination of lethal cyanotoxin concentrations that affect plant growth and development, is of primary importance.

Huang et al. (2009), provide evidence for two different morphological alterations in Tobacco BY-2 cells in exposure to MC-RR in two different concentrations. The exposure of Tobacco BY-2 cells to 60 µg mL⁻¹ of MC-RR was reported to show apoptotic morphological changes, including condensation of nuclear chromatin, cytoplasm shrinkage, and decreased cell volume. In contrast, 120 $\mu g\,mL^{-1}$ led to necrosis including rupture of the plasma membrane and the nuclear membrane and swelling of cells. Furthermore, many vacuoles with MC-RR detoxifying ability are significant in protecting vital cellular organs like the nucleus from cyanotoxin-related sub-cellular toxicity. These studies are evidence for the concentration-dependent phytotoxicity and plant species-dependent phytotoxicity of cyanotoxins. Furthermore, McElhiney et al. (2001) provide further evidence on this phenomenon, due to the complete inhibition of Solanum tuberosum growth at a concentration of 0.5–5 mg/kg MC-LR while the same observation was not reported for Phaseolus vulgaris when it was treated with the same MC-LR concentration. In the exposure of Daucus carota to CYN, no adverse effect on growth in the edible roots was reported by Guzmán-Guillén et al. (2017).



Fig. 1. Phytotoxic effects of cyanotoxins.

Table 4

Adverse effects of cyanotoxins in plants.

5	1			
Plant	Type of cyanotoxin	Cyanotoxin concentration	Effect on plant	Reference
Vicia faba (Beans)	MCs	100 µg/L	Reduction in germination rate	Lahrouni et al. (2012)
			 Reduction in the dry weight of shoots and roots 	
			 Reduction in total nitrogen content in roots 	
Daucus carota (Carrot)	CYN	50 µg/L	Reduction in plant mineral content	Guzmán-Guillén et al. (2016)
Triticum aestivum (Wheat)	MCs	100 µg/L	Inhibition of seed germination	Corbel et al. (2015)
Solanum lycopersicum (Tomato)			• Decreased the growth of primary root in high concentration	
Lactuca sativa (Lettuce)			• Decreased the growth of primary root in high concentration	
Oryza sativa (Rice)	MC-LR	500 μg/L	Inhibition of root elongation, crown root formation, and lateral root	(Cao et al., 2018a, 2018b,
			development from root primordia	2018c)
Oryza sativa	MC	500 µg/L	 Induced disruption of the antioxidant system and lipid peroxidation in rice 	Cao et al. (2018a, 2018b,
			roots	2018c)
Lactuca sativa	MC	2.5 μg/L, 6.5 μg/L	 Reduction in the total protein content 	Bittencourt-Oliveira et al.
			 Increase in antioxidant enzyme activity and rate of photosynthesis 	(2016)
Medicago sativa	MC-LR	100 μg/L	 Toxicity towards Actinobacteria, Gemmatimonas, Deltaproteobacteria, and 	El Khalloufi et al. (2016)
(Alfaalfa)			Gammaproteobacteria inhabiting the rhizosphere	
Spinacia oleracea	MC and/or	50 µg/L	 Growth inhibition in aerial parts (leaves) 	Llana-ruiz-cabello et al.
(Spinach)	CYN		 Alteration in Ca, K, and Mg concentrations in plant roots 	(2019)
Lactuca sativa		_	 Alteration in K levels of plant leaves 	
Lemna gibba	MCs	0.3 µg mL ⁻¹	 A decrease in plant growth and chl content 	Saqrane et al. (2007)
(Duckweed)			 Increase in peroxidase activity and phenol content 	
Cucumis sativus L.	MCs	100 μg/L, 1000 μg/	 Reduction in cucumber yield at the fruiting stage 	Zhu et al. (2018a, 2018b)
(Cucumber)		L	Reduction in vitamin C, soluble sugar, and organic acid contents in cucumber	
			fruits	

In contrast, Cao et al. (2018a, 2018b, 2018c), report a significant inhibition in root growth where root weight, length, surface area, and volume were observed to be reduced. Surprisingly, when *Lemna minor* L. was exposed to CYN, adverse effects were visible only in the first 24 h of exposure. Afterward, the plant gradually recovered from the phytotoxicity enforced by CYN. Therefore, the phytotoxicity differs for different cyanotoxins, the dosage of exposure and the genotype of the exposed plant species.

4.2. Influence on seed germination

Cyanotoxins can inhibit seed germination in many agricultural plants (Corbel et al., 2015; Lahrouni et al., 2012). Cyanotoxins are released from cyanobacteria due to stressful conditions, cell lysis, and death (Boopathi and Ki, 2014). Auxins have been shown to induce the release of the hormonal hold on seed germination, as demonstrated by "inactivation" studies based on auxin biosynthesis and auxin receptor genes (Liu et al., 2013). Furthermore, the dual binding ABSCICIC ACID

INSENSITIVE 3 transcription factor – which also binds to auxin-responsive elements has been implicated in the crosstalk between contrasting phytohormones (Nag et al., 2005). Therefore, there is a biochemical connection between ABA and auxins concerning seed germination. Seed germination can also be induced by endogenous factors such as reactive oxygen species (ROS) and as well as exogenous factors such as light and temperature, At the same time, nutritional compounds are also contributory factors (Skubacz and Daszkowska-Golec, 2017).

The studies focusing on the effect of cyanotoxins on seed germination have gained scientific attention due to the low field production and economic losses with the use of cyanotoxin-contaminated irrigation water (Saqrane and Oudra, 2009). However, the published research work based on actual field conditions is scarce. Pflugmacher et al. (2006) report the inhibition of seed germination in Medicago sativa exposed to MCs and ANTX-ain a cyanobacterial cell-free crude extract. Similarly, Vicia faba seeds showed a significant reduction in germination in exposure to MCs (Lahrouni et al., 2012). Furthermore, in the germination tests conducted by Corbel et al. (2015), Solanum lycopersicum, Triticum aestivum, and Lactuca sativa seeds were exposed to MCs, only the germination of T. aestivum was inhibited. These observations suggest that cyanotoxin exposure to crop plants via water irrigation can lead to a severe crop yield and quality threat, Under realistic conditions this could affect the food security and availability of organisms surviving within a particular r ecosystem. A study centered on the effect of cyanotoxins (cell-free extract of a Microcystis cyanobacterium) on seed germination of Pisum sativum, Lens esculenta, Zea mays, and Triticum durum demonstrated that there was a dose-dependent inhibition of seed germination of the above plant species, being P. sativum is the most sensitive while L. esculenta was the most stress-tolerant (Sagrane et al., 2009). The effect of cyanotoxin on seed germination may produce an additive effect with any other available contaminants in the system. Cao et al. (2018b) provide evidence for the inhibition of seed germination due to MCs in L. sativa occurring together with Cu. Moreover, according to this study, no significant inhibition was observed in seed germination in the absence of Cu.

Cyanobacteria trigger the production of endogenous abscisic acid (ABA) as a consequence of stress (Hartung, 2010). But the presence of cyanotoxins (biotic "toxin" stress) can elevate ABA levels in pre-germination seeds from seed plant species is a fundamental question in eco-toxicology. In the early "seedless" plants that colonized land, even minor levels of stress – such as mild drought – improved ABA production (Hartung, 2010). The attribution of allelopathy to water-based cyanotoxins, mainly in the growth inhibition of macrophytes such as *Ceratophyllum demersum* and *Myriophyllum spicatum*, unveils a new horizon in cyanobacterial research (Pflugmacher, 2002). Whether this allelopathy extends to a broad spectrum of angiosperm crop seeds is a worthy empirical question, especially with the rice grown in irrigated ecosystems worldwide.

4.3. Nitrogen and mineral uptake

The effect of cyanotoxins on the nitrogen uptake of plants is not well documented to date. Lahrouni et al. (2012), report the inhibition of root nodule formation and nitrogen assimilation in *Vicia faba* plants exposed to MCs. This effect could be due to the decline in the nitrogenase enzyme activity owing to MC accumulation. Similarly, a substantial variation in bacterial enrichment, diversity and relative abundances of taxa between bulk soil, rhizosphere, and *Medicago sativa* root tissues were reported due to exposure to MCs (El Khalloufi et al., 2016). Due to the strong interaction between plant health and bacterial interactions, the alterations in the microbiota of the soil rhizosphere could lead to severe implications in terms of inhibiting plant growth and development.

Concerning mineral uptake, cyanotoxin exposure can have both positive and negative consequences. As explained in the studies of Freitas et al. (2015), leaves of *Lactuca sativa* are observed to decrease the

mineral content in exposure to MCs and increase its mineral content in exposure to CYN in a time and concentration-dependent manner. Cao et al. (2017), report the stimulation of K and Ca uptake in plant roots to rise substantially with MCs, with a 47% rise compared to the control experiment. A significant decrease in Ca, Mg, K, and P in five days and Ca, Mg, K, P, Mn, Fe, Zn, Cu, and Mo after ten days was reported in lettuce leaves for all concentrations of MC exposure. In contrast, all the mentioned minerals were reported to increase in concentration after five days. After ten days, a further increase in Mn, Fe, Zn, Cu, and Mo was reported in lettuce leaves for all the concentrations of CYN exposure. Conversely, Guzmán-Guillén et al. (2016), note the reduction in mineral content of *Daucus carota* roots in exposure to CYN. Hence, the phytotoxic effects of cyanotoxins are prone to variation based on the plant's individual qualities and the toxin's identity.

4.4. Chlorophyll content and photosynthesis

The chlorophyll (chl) content in a plant is crucial in determining the photosynthetic capacity and plant growth. Thus, determine the effect of cyanotoxins on plant chl content and the rate of photosynthesis. McElhiney et al. (2001) report a sudden drop in chl content in *Solanum tuberosum* following exposure to MCs. Similarly, Saqrane et al. (2009) observed that the chl a and chl b content in *Zea mays* and *Lens esculenta* was reduced with exposure to MCs but not so in *Triticum durum* and *Pisum sativum* under similar regimes. However, *T. durum* experienced a reduction in leaf number, fresh weight, and plant height during 0.5 mg/mL MC exposure for 15 days, proving the species-specific nature of phytotoxicity created by cyanotoxins in plants.

Nevertheless, *Daucus carota* is reported to have no significant effects on photosynthesis when exposed to CYN at a concentration of 10 and 50 μ g/L (Guzmán-Guillén et al., 2016). Gutiérrez-Praena et al. (2014), report a decrease in the rate of photosynthesis in *Lycopersicon esculentum* in exposure to *M. aeruginosa* crude extracts containing an MC-LR concentration of 100 μ g/L. Surprisingly, a reduction in the photosynthetic rate was not observed when *L. esculentum* was exposed to pure MC-LR. These observations suggest an additive effect of cyanotoxin exposure with other contaminants or interferences in the *M. aeruginosa* crude extract in producing the observed outcome.

The study of Pereira et al. (2017), provides some interesting patterns of change in the chl and carotenoid content in Petroselinum crispum L. and Coriandrum sativum L. upon exposure to MCs and CYN. The chl a and chl b and carotenoid content in P. crispum L. decreased with exposure to MCs concentrations of 0.1 μ g mL⁻¹, 0.5 μ g mL⁻¹, and 1 μ g mL⁻¹. With exposure to CYN, the chl a and chl b and carotenoid content were not affected at an exposure concentration of 0.1 μ g mL⁻¹. However, at 0.5 μ g mL⁻¹ exposure concentration of CYN, the chl a and chl b and carotenoid content were observed to diminish compared to the negative control. Surprisingly, at 1 $\mu g\ m L^{-1}$ of CYN, the pigment content in P. crispum L increased. Furthermore, chl a, chl b, and carotenoid contents in P. crispum L were influenced by the type of cyanotoxin and the exposed cyanotoxin concentration. Concerning Coriandrum sativum L., the chl a chl b, and carotenoids contents were reported to have increased at lower MC exposure concentrations of 0.1 μ g mL⁻¹ and 0.5 μ g mL⁻¹. In the same study, it was shown that chl a and chl b continued to increase at $1~\mu g~mL^{-1}$ concentration, but a decrease was observed in the carotenoids. CYN exposure to C. sativum L. at a concentration of 0.5 $\mu g\ m L^{-1}$ increased the concentration of chl b and chl a but also induced a decrease in the concentration of carotenoids. The alterations in the chl content will provide adverse effects to the growth, development, plant yield, and defence mechanisms in terms of phytotoxicity. Furthermore, these studies provide evidence for the concentration-dependent activity of cyanotoxins.

Besides the alterations in the level of photosynthetic pigments, phytotoxicity created by the uptake of cyanotoxins in plants leads to several plant defects in photosynthesis. The cyanotoxin uptake into plant cells alters the membrane permeability. Cordeiro-Araújo et al.

(2016) report an enhanced plasma membrane electrical conductivity in the leaves of Lactuca sativa and Eruca sativa upon exposure to M. aeruginosa extract comprising MC in a concentration and time-dependent manner. This intern affects the electrical properties of the plasma membrane that control the exchange of ions across the membrane (Máthé et al., 2021). In terms of photosynthesis, the altered membrane permeability in plant cells could affect the exchange of essential minerals like Mg²⁺ which is crucial in chl synthesis and activity of the light reaction of photosynthesis. Similarly, many studies reported that the CO₂ uptake levels and the overall photosynthetic rate in plants are affected by cyanotoxin exposure in positive or negative aspects. According to Bittencourt-Oliveira et al. (2016), the CO₂ uptake and the overall photosynthetic rate were observed to be enhanced in L. sativa exposed to MC-LR and MC-RR contaminated irrigation water. However, the highest exchange of CO₂ was reported at low concentrations of MC exhibiting antagonistic effects on CO₂ uptake in L. sativa plants upon increased MC exposure concentrations. Similarly, Gutiérrez-Praena et al. (2014), provided similar evidence concerning Lycopersicon esculentum where enhanced CO₂ uptake and carbon fixation are reported upon exposure to MC-LR. The enhanced photosynthetic rate in these studies could be attributed to the increased demand for energy within the plant upon cyanotoxin entry, protecting itself from ROSand activating defense mechanisms. Therefore, even though these studies exhibit an enhanced rate of CO₂ uptake and photosynthesis rate upon cyanotoxin exposure, extended exposure time and concentration of cyanotoxin could lead to extensive retardation in the CO₂ uptake and the overall photosynthesis rate.

Additionally, the plant uptake of cyanotoxins interferes with photosynthesis by altering the activity of photosystem I (PSI) and photosystem II (PSII), a possibility of leading to inhibition of the electron movement associated with reaction centers excitation (Maxwell and Johnson, 2000). In a study conducted to determine the effect of MC-LR on the activity of cyanobacteria it was reported that the activity of both PSI and PSII and the redox coupling between photosystems were drastically reduced by exposure to MC-LR exposure. Moreover, due to the severe reduction in ATP synthesis, vital cellular functions, including respiration and N_2 fixation, were reported to be decelerated (Sharma and Rai, 2013).

As above mentioned studies, a similar study was conducted by analysing the maximum quantum yield of PSII (Maxwell and Johnson, 2000). Gutiérrez-Praena et al. (2014) measured the maximum fluorescence yield of Photosystem II, a decreased activity of PSII was reported in Lycopersicon esculentum leaves when exposed to a crude extract of M. aeruginosa containing 100 µg/L MC-LR. Similarly, the same study reported an overall reduction in the photosynthetic efficiency within the exposure period. In parallel, Sagrane et al. (2009), reports photo-inhibition in Triticum durum, Zea mays, Pisum sativum and Lens esculenta on exposure to MC containing extract from a cyanobacterial bloom comprising of MC-RR and MC-LR owing to the retarded PSII activity. The decline in PSII activity of the plants was dependent upon the cyanotoxin dose and the specific plant species. These studies provide evidence for the impaired PSII activity and the overall photosynthetic efficiency of crop plants on exposure to MC. Contrarily, Guzmán-Guillén et al. (2016), reported an enhanced PSII activity of Daucus carota exposed to Chrysosporum ovalisporum extract in a concentration of 10 and 50 µg CYN/L. Furthermore, the same study demonstrated an increased overall photosynthetic efficiency in the plants under study.

Moreover, Llana-ruiz-cabello et al. (2019), reported no alteration in the activity of the PSII system in *Spinacia oleracea* and *Lactuca sativa* upon exposure to MC, CYN, or MC + CYN mixture. Different factors govern the effect of cyanotoxins on photosystem activity and the photosynthetic rate. These include cyanotoxin, exposed plant species, and exposure time and concentration. The phytotoxicity created upon cyanotoxin uptake affects photosynthesis by interfering with photosynthesis's light and dark reactions. This is mainly achieved by altering the expression of the key enzymes associated with the light and dark reactions of photosynthesis. A study conducted by (2014), using leaf proteome studies of Lacuta sativa on exposure towards MC and CYN, reported an extensive reduction in the synthesis of enzymes that are crucial in driving the light-dark reactions of photosynthesis. The reduction led to a decline in the overall photosynthetic rate. Exposure to MC and CYN inhibits many enzymes associated with photosynthesis, such as oxygen-evolving enhancer proteins, quinone oxidoreductase, chloroplast PsbO4, chlorophyll a-b-binding proteins, and ferredoxin-NADP reductase participating in the light reaction of photosynthesis and ribulose-1,5-bisphosphate carboxylase/oxygenase activase (RuBP activase), phosphoribulokinase (PRK), sedoheptulose-1, 7-bisphosphatase (SBPase and ribulose bisphosphate carboxylase/oxygenase activase 1 (RuBisCO activase 1) participating in the Calvin cycle.

4.5. Effects on oxidative stress

The exposure of plant and animal cells to cyanotoxins results in the generation of ROS (Chen et al., 2012a, 2012b; Redouane et al., 2019). They exhibit an intense reactive ability with cellular compounds such as lipids, proteins, and DNA. In plants, the adverse effects of these ROS are relieved by the well-equipped antioxidative defense system. This antioxidative defence system in plants includes enzymes catalase, ascorbate peroxidase, superoxide dismutase, in addition to then on-enzymatic antioxidants (Peuthert et al., 2007; Sagrane and Oudra, 2009). Enhanced oxidative stress is observed in most plants with the uptake of cyanotoxins. However, studies conducted on oxidative stress induced by cyanotoxins under actual field conditions are sparse. A study conducted by Chen et al. (2012a, 2012b), reported a significant rise in the amount of ROS in the roots of Oryza sativa plants collected from a natural ecosystem (Taihu Lake region, China) in comparison to the controls. Corbel et al. (2015) reported the increase in oxidative stress of Solanum lycopersicum, Triticum aestivum, and Lactuca sativa when exposed to an M. aeruginosa (strain PCC7820) crude extract containing 14 MC variants. In the same experiment, the exposure of lettuce to the crude extract of M. aeruginosa down-regulated the glutathione S-transferase activity. It up-regulated the activities of superoxide dismutase, catalase, and peroxidase activities as an antioxidant response from MC exposure. The development of anti-oxidative responses against increased oxidative stress caused by cyanotoxins can be designated as a defense mechanism in plants against the phytotoxicity created by cyanotoxins. Similarly, Cao et al. (2018a, 2018b, 2018c) reported the development of oxidative stress and lipid peroxidation in rice roots following exposure to 50 µg L^{-1} and 500 µg L^{-1} MC concentrations. This indeed resulted in a drastic reduction in the root activity of plants, which may be correlating with the plant yield. Conversely, Pereira et al. (2017), reported no induction of oxidative stress when Petroselinum crispum L. and Coriandrum sativum L. were exposed to both MC and CYN in the concentrations of 0.1 μ g mL^{-1} , 0.5 µg mL^{-1} , and 1 µg mL^{-1} at ten days of exposure.

5. Effects of cyanotoxins on human health

5.1. Health risk

The formation of harmful cyanobacterial blooms enhances the risk of surface freshwater contaminations, leading to significant health issues in humans and animals. Cyanobacterial toxicity is highly influenced by dependency on stored water sources like reservoirs, rivers, groundwater wells, and tanks where cyanotoxin contaminations are frequently identified. As mentioned throughout this review, cyanotoxincontaminated irrigation water for agriculture is the most frequent cyanotoxin entry route into croplands. This provides the entryways of cyanotoxins to humans in the accumulation of cyanotoxins in edible plants. Similarly, humans may be unintentionally exposed to cyanotoxins through drinking water or by ingesting cyanotoxin-contaminated water during recreational activities. Accompanying, the likelihood of cyanotoxin penetration through the human skin by dermal exposure during recreational activities is still under debate and requires serious investigations (Nielsen and Jiang, 2020). This section reviews the adverse health impacts of cyanotoxin intoxications in humans.

MCs and nodularin are the most commonly occurring cyclic pentapeptides produced by cyanobacterial blooms. According to the WHO provisional guideline (World Health Organisation, 2017), only a value of less than 1 µg/L for microcystin-LR (free plus cell-bound) is permitted in drinking water (Vankova et al., 2019). MCs, due to their hydrophilic nature, influence the cellular uptake by organic anion transporting polypeptides (OATPs), and such transporter molecules are expressed tissue-specifically (Svirčev et al., 2017) MCs employ diverse cellular mechanisms in inducing severe organ impairments. These include enhanced oxidative stress, cytoskeletal disruption, endoplasmic reticulum dysfunction, mitochondrial dysfunction, DNA damage, and apoptosis (Cao et al., 2019; Xu et al., 2020). The chronic exposure of MCs in humans tends to activate the diacylglycerol (DAG) pathway resulting in the activation of B cell lymphoma 2 (Bcl-2) protein and protein kinase c (PKC) which could lead to tumor formation (Svirčev et al., 2017). However, the unabsorbed MCs are not chemically altered, only transported to the intestine and removed out with feces or else excreted out with bile in the liver (Li et al., 2014). MCs can move to vital cellular organs such as the brain, heart, and lungs, which could lead to chronic toxicities in the human body (Menezes et al., 2013; Welten et al., 2019). The liver is one of the key targets of MC in the human body (Massey et al., 2018). A study conducted by Chen et al. (2009), has identified a chronic level of liver damage in a group of fisherman exposed to MCs by consuming contaminated fish.

Furthermore, it is reported that MCs can move through the bloodbrain barrier in humans, resulting in unexpected chronic damage (Fischer et al., 2005; Massey et al., 2018). Liver cancer, glycogen depletion, and hepatocyte necrosis are the significant effects of MC toxicity (Drobac et al., 2016). The extensive liver damages could lead to the inability to synthesize bile pigments ultimately internal bleeding or death due to haemorrhagic shock (Badar et al., 2017). Extensive expression of OATPs in the human liver facilitates the active uptake of MCs into liver cells, leading to the selective liver toxicity of MCs (Fischer et al., 2005; Massey et al., 2018). This is the reason why MCs are categorized under the umbrella of hepatotoxins. The MC toxicity is preliminarily induced by inhibiting the activity of protein phosphatases (Xu et al., 2020). As reported in a study conducted by Yang et al. (2018), using human liver cell lines and high throughput sequencing techniques, significant inhibition of protein phosphatase 2 enzyme activity upon MC-LR exposure is observed. Similarly, the same study reports that MC-LR exposure alters the expression of microRNAs in the liver cells inducing severe liver injuries and promoting the formation of liver tumours. Similarly, the presence of OATP receptors is reported from cell lines of the liver, colon, and pancreatic tumours (Vankova et al., 2019), which explains these organs as possible sites in determining MC toxicity.

Furthermore, Ma et al. (2017), provide evidence for a similar study where the miRNA expression profile of HepG2 cells was altered due tothe in-vitro delivering of MC-LR. Therefore, as suggested, the miRNA expression affected by the MC-LR exposure negatively affect in liver toxicity. The capability of MC transfer from mother to progeny in mammals at the stage of pregnancy and the ability of maternal MC in creating liver toxicity of the offspring is still under debate. However, a study conducted using pregnant rats injected with MC-LR has provided evidence for the accumulation of MC-LR in the liver of neonatal rats (Zhao et al., 2016). The transfer of MC-LR from mother to newly born offspring in mammals was explained in this study. The reproductive toxicity of MC-LR has equally gained scientific attention concerning the adverse effects associated with reproductive health in animals. MC-LR reproductive toxicity is associated with impairing the structure and function of reproductive organs including ovaries, placenta, prostate gland, and testes leading to reduced fertility (Zhang et al., 2021). Similarly, the MC transmission through the placenta to the embryo

could lead to malformation, organ dysfunction, and growth retardation or death of the offspring (Zhang et al., 2021).

The kidney is another target of MC toxicity in humans. Severe cytotoxic effects are induced in the renal tissues owe to the MC toxicity in humans. A study conducted by Piyathilaka et al. (2015), using human kidney cell lines provides evidence for reduced cell viability and a significant upregulation in the genes involved in apoptosis upon treating with MC-LR. Furthermore, several studies were published concerning the renal toxicity of MCs conducted using animal models (Badar et al., 2017; Drobac et al., 2016; Feng et al., 2017; Huang et al., 2015). Chronic exposure to MCs lead to adverse health effects in the human gastrointestinal tract and vital organs of the digestive system (Kubickova et al., 2019).

Several studies report the potential of MCs in contributing to colon cancer progression. As reported in Miao et al. (2016), MC-LR promotes the migrative and invasive potential of colorectal cancer by the upregulation of the matrix metallopeptidase-13 gene. Similarly, as reported in Zhu et al. (2018a, 2018b), MC-LR can enhance the migrative potential of colon cancer by activating the expression of cadherin-11 responsible in the homophilic cell to cell adhesion of cancer cells. In parallel, MC toxicity promotes colon cancer progression by the upregulation of specific micro RNAs and the activation of STAT3 genes equipped with the instructions required for protein synthesis (Ren et al., 2019). These studies manifest the potential of MCs in promoting the same toxicological outcome in diverse mechanisms. MC toxicity imposes a severe threat to many of the vital organs in the human body. However, studies and experimental data are required to fill the gaps and the risk assessment associated with MC toxicity.

The highly water-soluble and extracellular nature of CYN makes humans more susceptible to CYN exposure. The human liver and intestine are the organs induced with CYN cytotoxicity. Similarly, CYN imposes its cytotoxic effects on the heart, lungs, kidney, and eyes (Yang et al., 2020). CYN is well known as a short-term toxic agent. CYN creates diverse impairments in the human body. These can exert cytotoxicity, immunotoxicity, genotoxicity, and endocrine toxicity by suppressing the protein synthesis, inducing DNA damage by enhanced oxidative stress, and affecting acetylcholinesterase (AChE) activity by binding with the estrogen receptors (Yang et al., 2020). The rapid toxicity created by CYN in response to the metabolites generated by the CYP450 system and the long-term toxicity could lead to the irreversible inhibition of protein synthesis (Vankova et al., 2019; Yang et al., 2020). Cytotoxicity induced by CYN is specified concerning the cellular alterations, suppressed cellular proliferation, and induced apoptosis leading to hindered cell viability and cell death in a time and concentration-dependent manner (Pichardo et al., 2017). Similarly, concerning the cell cycle, CYN imposes the downregulation of genes involved in the progression of the cell cycle causing the accumulation of G1/S and G2/M cells in the synthesis phase and the growth phase of the cell cycle leading to DNA damage and cell death (Huguet et al., 2019). As reported in the studies conducted by Vanova et al. (2019), CYN treatment produced a detrimental effect in the differentiation of hepatic cells from the human embryonic stem cells by a substantial disruption of the liver tissue homeostasis.

Furthermore, CYN suppresses the synthesis of antioxidants including glutathione, leading to enhanced oxidative stress worsening the risk associated with cytotoxicity (Huguet et al., 2019). Poniedziałek et al. (2015), provide evidence for the potential of CYN in inhibiting the activity of antioxidant enzymes and restricting the development of lymphocyte cells by enhancing the ROS levels. The enhanced cellular oxidative stress could further encourage DNA destruction and apoptosis. A mixture of MC-LR and CYN produced more chronic genotoxic damages than the individual extent of damage (Díez-Quijada et al., 2020; Gutiérrez-Praena et al., 2019; Hercog et al., 2016). Hercog et al. (2016), studied the effect of CYN and MC-LR alone and the mixture of CYN and MC-LR in the mRNA expression of some selected genes. The expression level of mRNA to the CYN and MC-LR mixture was similar to the effect of CYN alone, which indicates the high genotoxicity exhibited by CYN.

Cyanotoxin activity in the human body can induce tumours in vital organs such as the liver, heart, lungs, and kidney. Similarly, some potential cyclic peptides' anticancer properties and CYN are is also under study, which could provide some positive expectations concerning cancer therapy (Vankova et al., 2019).

5.2. Implications on CKDu in Sri Lanka

The prevalence of chronic kidney disease of unknown etiology (CKDu) has been reported from diverse regions around the globe including Sri Lanka, India, El Salvador, Guatemala, Brazil, Mexico and Costa Rica, Honduras (Redmon et al., 2021), and Egypt (Weaver et al., 2015). It is reported to be asymptomatic till late stages, slowly developing within the body of the patient, and is irreversible. Several occupational and non-occupational risk factors are considered in CKDu incidence. However, the exact cause linked with the CKDu incidence is still unknown (Anand et al., 2019; Redmon et al., 2021). Notably, Liyanage et al. (2016), reported the occurrence of potential cyanotoxin-producing cyanobacteria and cyanotoxins from water samples collected from, Giradurukotte, Sri Lanka. This region is one of the highest CKDu prevailing areas in Sri Lank and,. raises whether cyanotoxins are acting as a potential risk factor for CKDu incidence. Furthermore, the North Central and North Western provinces of Sri Lanka reports a high incidence of CKDu from the latter part of the 20th century. Manage (2019), reports the extensively high concentration of CYN in the urine samples collected from CKDu patients from the North Central province of Sri Lanka, which further provides evidence for possible cyanotoxin intoxications in CKDu patients.

As reported by Svirčev et al. (2017), most of CKDu patients in Sri Lanka are fulfilling their drinking water requirements by shallow wells or reservoirs, which are reported to have significant domination of cyanobacterial blooms. Furthermore, Magana Arachchi and Liyanage (2012), observed the presence of cyanotoxin-producing cyanobacteria in Kala Wewa located in Anuradhapura, in the North-central province of Sri Lanka, which records a substantial number of CKDu patients. In a field study conducted by Wijewickrama and Manage (2019), a significant accumulation of MC-LR was observed in hybrid rice variety BG358 and Ipomea aquatica irrigated from cyanotoxin contaminated water obtained from Padaviya reservoir in Padaviya, Sri Lanka. However, the mean potential human exposure of MC-LR in I. aquatica is 0.03 \pm 0.01 µg/kg of body weight/day which is lesser than the WHO recommended daily intake of 0.04 µg/kg of body weight/day. Conversely, hybrid rice variety BG358 was reported to have a potential human exposure of MC-LR as 0.10 \pm 0.01 $\mu g/kg$ of body weight/day which is significantly higher than the WHO recommended daily intake. Furthermore, Sri Lanka consumes rice as the primary staple food, and North Central province is a high-risk zone in CKDu incidence. Therefore routine monitoring of the cyanotoxin contaminations in food and water used for irrigation is essential even though cyanotoxins are not yet confirmed as potential agents for CKDu incidence. These observations correlate with the numerous adverse health impacts experienced by the people living in the dry zone of Sri Lanka. Accordingly, more extensive and elaborate studies should be conducted to unravel the relationship between cyanotoxins and CKDu in Sri Lanka.

6. Future perspectives

The extensive distribution of toxic cyanobacterial blooms severely imposes agricultural productivity and human health challenges. According to the available literature, cyanotoxins can affect agricultural plants, even at biochemical or molecular levels. However, most studies on cyanotoxin accumulation in plants were conducted in synthetic hydroponic conditions with higher cyanotoxin concentrations than in natural environmental conditions. This may provide an overestimation about the cyanotoxin accumulation in plants as the cyanotoxin uptake in natural systems is affected by many factors. Some of those include the adsorptive effects of soil particles, the potential biodegradation, photolysis, and hydrolysis.

Additionally, in realistic conditions, certain plants' antioxidant and mineral levels observe to rise to overcome the oxidative stress due to the cyanotoxin uptake. Therefore, it is evident that further studies on cyanotoxin accumulation should be conducted based on natural conditions rather than concentrating on laboratory experiments to determine the realistic factors concerning cyanotoxin accumulation. Similarly, the information regarding the period of persistence of cyanotoxins in agricultural soils is scarce. Knowledge of cyanotoxin persistence is evident concerning groundwater contamination, more specifically in areas where contaminated water is used for agriculture. As mentioned in several studies, cyanotoxins tend to absorb by roots and transported to the grains and fruits via the shoot. However, the cyanotoxin concentrations detected in fruits or grains were severely lower than those in roots. This may be due to the partial metabolism of cyanotoxins in transporting through the shoot into the fruits. Therefore, further studies are recommended to identify the uptake and fate of cyanotoxins within the crop plants.

Furthermore, most toxicity studies on plants and humans have been performed on MCs. It is high time for scientists to follow up the MC toxicity landscape while not neglecting the induced effects of other/ lesser cyanotoxins. Besides, studies should be performed on cyanotoxins influence on livestock, fish stocks, and poultry. It is also time to develop a suitable numerical or color-coded scale for toxins, concerning cyanobacterial species, season, waterbody, type of toxin, and biomonitoring systems that can document the level of potential exposure. Prevention is better than cure, and that should be the motto of the scientific community to ensure cyanotoxin-related events are minimal, if not rare.

The accumulation of cyanotoxins in edible crop plants is one of the major routes to food chains. Consumption of these could lead to ultimate health hazards in humans. It is disconcerting that rice grains, both human-bred and traditional, have been shown to contain some degree of cyanotoxin contamination. Rice is also the staple food in most Asian countries, including the people living in Sri Lanka and India. Therefore, researchers should pay more attention to the uptake mechanism and storage of cyanotoxins in rice plants. The accumulation of cyanotoxins in grains like wheat and barley could also lead to severe impacts in many European countries owing to high daily consumption. A systemic study of agriculture ecosystems (irrigated against rainfed) and their basal and plant-based levels of cyanotoxins need immediate attention.

Therefore, the study of cyanotoxin uptake and persistence in edible plant parts is of prime importance. Furthermore, public awareness of the consequences of consuming cyanotoxin contaminated food material or cyanotoxin contaminated water for irrigation and drinking purposes will help control the rising numbers of patients with severe illnesses due to cyanotoxin intoxications such as cancer. Similarly, scientific investigations regarding the involvement of cyanotoxins in CKDu incidence should be globally addressed. In this review, we report the studies on the presence of significant cyanotoxins in water and soil, their uptake into plants and accumulation in plant parts, and the toxic effects on biota. Knowledge gained from the present review will help design and implement cyanotoxin control strategies to minimize adverse toxicity.

Author contribution

Chanusha Weralupitiya: Formal analysis and investigation, Writing original draft preparation. Rasika Wanigatunge: Formal analysis and investigation, Writing - review and editing. Dilantha Gunawardana: Writing - original draft preparation, Writing - review and editing. Meththika Vithanage: Conceptualization, Funding acquisition, Writing review and editing. Dhammika Magana-Arachchi: Conceptualization, Funding acquisition, Writing - review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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