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Review

An overview of the accumulation of microcystins in aquatic ecosystems

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ABSTRACT

Cyanotoxins produced by toxic cyanobacteria pose a major, worldwide environmental threat to freshwater ecosystems. Microcystins (MCs) are considered to be the most hazardous groups. Indeed, some of the largest aquatic ecosystems on the earth are being contaminated with MCs. Questions have arisen regarding their transfer and bioaccumulation in natural environment. This review summarizes the present state of knowledge regarding toxic cyanobacteria and MCs, with a specific focus on their distribution in different components of aquatic ecosystems. Their accumulation in water columns, aquatic animals, plants, and sediments is summarized. MCs have been contaminating all areas of the aquatic ecosystems. Of these, the water column was the most contaminated with MCs and served as an intermediate transmission substation. Via this route, MCs could enter to other stations such as sediment, animals, aquatic and terrestrial plants. Therefore, the use of water contaminated with MCs may induce food chain contaminations with considerable health risks.

Contents

1. Introduction

The occurrence of toxic cyanobacteria blooms associated with their toxins in aquatic ecosystems has become a worldwide problem (Preece et al., 2017). The impacts of these toxins on human health have been exacerbated as a result of increased nutrient loading and climate change (Preece et al., 2017). Among cyanotoxins, microcystins (MCs) with their hepatotoxic and tumor-promoting activities, are the most common and are considered to be one of the most hazardous groups (Li et al., 2017). MCs can be produced by numerous genera, *Anabaena* (*Dolichospermum*), *Aphanizomenon*, *Microcystis*, *Planktothrix* and more rarely by

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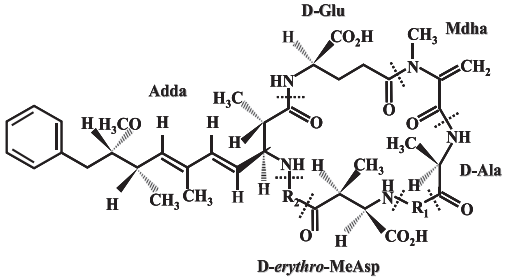
Anabaenopsis, Aphanocapsa, Cylindrospermopsis, Fischerella, Gleotrichia, Gomphosphaeria, Hapalosiphon, Nodularia, Nostoc, Phormidium, Pseudanabaena, Synechococcus, in which *Microcystis* genus has been reported as the most common bloom forming and the main producer of MCs in freshwater ecosystems (Preece et al., 2017). MCs contain seven peptide-linked amino acids, with the two terminal amino acids of the linear peptide being condensed (joined) to form a cyclic compound. As a group of cyclic heptapeptides, MCs share a general structure of cyclo-(D-alanine-R_1-D-MeAsp-R_2-Adda-D-glutamate-Mdha) in which R_1 and R_2 are variable L-amino acids, D-MeAsp is D-erythro-β-methylas-partic acid, and Mdha is N-methyldehydroalanine (Preece et al., 2017). Among MCs congeners, the three most predominant ones are MC-LR, MC-RR and MC-YR, in which MC-LR is the most toxic one (Li et al., 2017). The R1, R2 variable amino acids for MC-LR, MC-RR and MC-YR are leucine (L), arginine (R) and tyrosine (Y) (Fig. 1). The amino acid Adda, or (2S,3S,8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid, which present in all variants, is crucial for the toxicity of MCs molecules. Over 100 structure variants have been reported so far (Li et al., 2017).

The ecological risk of MCs in the aquatic ecosystems is a growing concern. Toxic effects of MCs on animals and plant have been extensively studied and reviewed (Corbel et al., 2014; Chen et al., 2016; Elisabete et al., 2016; Machado et al., 2017; McLellan and Manderville, 2017). Target molecules of MCs appear to be the same in both animals and higher plants. In mammal cells, MCs able to enter in hepatocyte cell membranes through active uptake by multispecific organic-anion transporting polypeptides (OATP) and concentrate mainly in liver (McLellan and Manderville, 2017). However, the specific transporters of these in vegetable organisms are not known. It is suggesting that peptide transporters might potentially be involved in the transport of MCs in higher plants (Machado et al., 2017). The inhibition of protein phosphatases (PP) 1 and PP2A is widely assumed as the principal mechanism of toxicity of MCs, however recently studies found that MCs modulate PPs activity not only by direct inhibition of their activity, but also by regulating their expression (Chen et al., 2016; Elisabete et al., 2016). While PPs serve as a regulator to maintain homeostasis in the cell, inhibition of PPs leads to hyperphosphorylation, causing severe cell damage (Chen et al., 2016). This is a major post-transitional modification which can result in excessive signaling and may lead towards cell proliferation, cell transformation and tumor promotion (Elisabete et al., 2016). Besides inhibition of PPs, oxidative stress produced by reactive oxygen species (ROS) such as superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($HO^{\bullet}$) may play an important biochemical mechanism of MCs toxicity in both mammal and plant cells (Elisabete et al., 2016).

For many years, the occurrence of cyanobacterial blooms associated with MCs in drinking water has resulted in a number of public health events. Exposure to these toxins can lead to liver failure in wild animals, livestock and aquatic organisms, as well as human illnesses and deaths. The most well-known occurrence of a harmful effect of MCs is sometimes referred to as “the Caruaru Incident”. This event represents the first confirmed 70 deaths at a hemodialysis center as a result of direct exposure to MCs (Pouria et al., 1998). Ueno et al. (1996) also reported that human chronic exposure to MCs via consumption of drinking water contaminated with MCs has increased risks of primary liver cancer in humans in the eastern region of China. In a study by Chen et al. (2009a), a human population (in China) was chronically exposed to MCs via consumption of contaminated aquatic organisms. The authors reported that there was a positive relationship between the MCs concentration in serum samples and major liver biochemical indices, confirming hepatocellular damage. Many deaths of terrestrial and aquatic animals due to acute exposed to MCs have been reported. As a preventive step to reduce risks caused by MCs, the WHO recommends a provisional guideline value of 1 $\mu g\, l^{-1}$ for MC-LR concentration in drinking water and a chronic tolerable daily intake (TDI) of 0.04 $\mu g\, kg^{-1}$ body mass per day for human consumption (Li et al., 2017).

Bioaccumulation and distribution of MCs in different aquatic organisms has been extensively studied and reviewed (Martins and Vasconcelos, 2009; Ferrão-Filho and Kozlowsky-Suzuki, 2011; Corbel et al., 2014; Machado et al., 2017; Preece et al., 2017). Such



	R_1	R_2
microcystin-RR	arginine	arginine
microcystin-LR	leucine	arginine
microcystin-YR	tyrosine	arginine

Fig. 1. Chemical structure of the three most common microcystin (MC) analogs (MC-LR, - RR, -YR).

reports suggest a potential risk to higher trophic level species, including humans. However, reports on the interrelation and distribution of MCs in aquatic compartments are scarce. While a number of studies have looked at the temporal and spatial variability of MCs in water and living organisms, the spatial distribution and accumulation of MCs in lake sediment has not been discussed to the same extent. Moreover, the interaction and distribution of MCs in different aquatic compartments such as water column, sediment, living organisms has been rarely discussed. Therefore, the central aims of this review are to summarize and discuss the interrelation, dynamics and distribution of MCs in different compartments of the aquatic environment, including aquatic animals, plants and sediment. Furthermore, based on recent data, this review provides an updated review of MC accumulation, including a comparison to the ones published previously, which may shed new insights on possible directions for future study of MCs accumulation.

2. Interrelation of microcystins in different aquatic phases

Microcystins are first produced and retained in cyanobacterial producer-cells (intracellular) with usually more than 95% of the toxin contained within healthy cells during the growth and steady phase of blooms. However, these intracellular toxins are eventually released into the surrounding water body (extracellular) during senescence and lysis at the end of blooms, which leads to the accumulation of a high concentration of dissolved MCs in the water column (Zhang et al., 2009). The ambient concentration of dissolved MCs has resulted from several factors such as environmental factors, dilution, photodegradation, adsorption to solid particles including living organisms and biodegradation (Song et al., 2015). In fact, there is a strong correlation between MCs concentration in water (aqueous phase) and MCs concentration in cyanobacterial scum (solid phase) (Zhang et al., 2009; Paldavičienė et al., 2015; Xue et al., 2016). However, recent studies revealed that MCs only originate from toxigenic strains of a few species, thus total MCs concentration generally positively correlated with toxigenic cyanobacterial biomass (Dong et al., 2016; Hu et al., 2016).

The fate of MCs at the end of bloom event can include dilution with the water surrounding, deposition on sediments, biodegradation, and/or transfer into aquatic organisms (Fig. 2). As a result of these processes, MCs in the aquatic environments are mainly of four types: cell-bound toxins in cyanobacterial cells, dissolved toxins in water surrounding, bio-accumulated toxins in organisms, and accumulated toxins in sediment or conjunct toxins with suspended substances (Song et al., 2015), and exist both in solid phases (cell bound forms, accumulated in living organism or absorption in sediment) and in aqueous solution (dissolved forms) (Fig. 2).

Aquatic animals can bioaccumulate MCs via two main routes: by feeding on toxic cyanobacterial cells and cyanotoxin-containing food (transfer from solid to solid phase) or by uptake of dissolved MCs in surrounding water (transfer from aqueous to solid phase). Many aquatic animals, including fish, shrimps, gastropods and bivalves, have been shown to accumulate MCs in their tissues (Ferrão-Filho and Kozlowsky-Suzuki, 2011; Schmidt et al., 2013; Ferrão-Filho et al., 2014). Among the food chains, these toxins can be transferred to higher trophic levels, even to human beings (Sotton et al., 2014; Preece et al., 2017). In planktivorous animals, MCs accumulated in their tissues through ingestion of toxic cyanobacterial cells in their diet or via food webs transfer is considered the main route of MC accumulation (Ferrão-Filho et al., 2014). When examined the relationship between the MC concentrations in the diet and in consumers, several studies revealed that higher MC concentrations in diets resulted in higher MC concentrations in consumers, suggesting a direct transfer (Zhang et al., 2009; Ferrão-Filho et al., 2014; Xue et al., 2016). In a laboratory experiment, Schmidt et al. (2013) reported that more than 80% of the free MCs in the water fleas *Bosmina* fed to the pumpkinseed sunfish *Lepomis gibbosus* was directly transferred to the sunfish. Although biodilution is the dominant process in most aquatic species, several organisms such as zooplankton and zooplanktivorous fishes showing some potential for biomagnification (BMF) (Kozlowsky-Suzuki et al., 2012). In general, the transfer or accumulation of MCs from phase to other phases in aquatic ecosystem is likely to be depended on a number of factors, such as the MCs concentration in the initial phase, mode of transfer as well as biodilution capacity.

Aquatic plants generally have the ability to biotransform toxic substances into less toxic compounds which are finally stored in vacuoles of storage cells (Romero-Oliva et al., 2014). Therefore, they

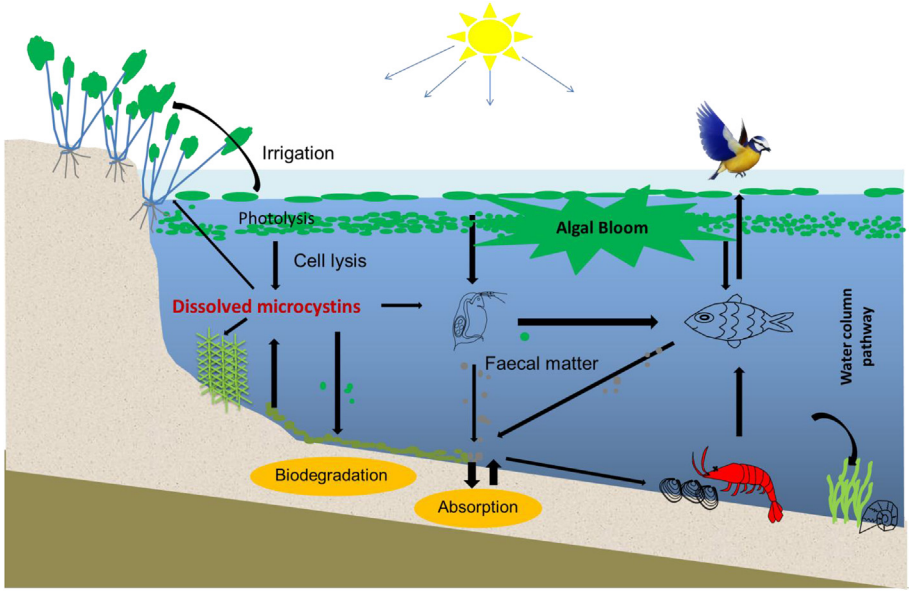


Fig. 2. A schematic showing bioaccumulation and transfer of microcystins (MCs) in aquatic ecosystem (Modified from Song et al., 2015).

have been considered to be potent phytoremediators. Although the ability of MCs to enter the food chain via agricultural crops has been observed in several studies, the interrelation of MCs in aqueous phase and in plant tissues has not been thoroughly understood. Previous investigations have shown that toxin concentrations accumulated in plants correlated positively with MCs concentrations in irrigation water. Suggesting that higher MCs concentration in aqueous phase will result in greater MCs concentration in plants (Mohamed and Al-Shehri, 2009; Chen et al., 2012). Terrestrial plants, including many crop plants, do not directly contact with MCs and cyanobacterial blooms from water, they are exposed to MCs via irrigation with water containing cyanobacterial blooms and toxins. The concentration of MCs in surface waters used as irrigation source up to 6500 $\mu g\,l^{-1}$ has been reported (Corbel et al., 2014). Recent studies evidence that the irrigation of crop plants with water contaminated with cyanotoxins not only inhibits growth of plants, but also can induce a food chain contamination with a considerable health risk (Chen et al., 2012; Corbel et al., 2014). However, there is still limited information on the persistence of MCs in both irrigation water and soil, as well as their mode of transfer and bioaccumulation into agricultural plants. Therefore, further scientific research is needed into the uptake and transfer of MCs from soil to plant as well as their fate and interrelation in terrestrial environment.

In aquatic systems, MCs can be present not only in water, in living organisms but also in lake sediments. Previous studies have indicated that MCs in sediments came from several main processes including the sedimentation of cyanobacterial cells including MC-containing fecal pellets from water column, transfer or/and adsorption of dissolved MCs to benthic phase and the production of benthic cyanobacteria (Fig. 2) (Song et al., 2007; Chen et al., 2008). The sedimentation rates for MC-containing particles during the bloom period have been reported up to 2.53 $mg\,m^{-2}$ d. Therefore, lake sediment is considered as a major destination for MCs (Wörmer et al., 2011). The accumulation of MCs in lake sediments has been considered as a potential hazard to benthic organisms. An earlier report indicated that sediments contained two kinds of MC fractions, including a loosely adsorbed and therefore “readily extractable” fraction, and a bound fraction of pellets (Chen et al., 2008). Both these forms may re-dissolve back into the water phase (Mohamed et al., 2006). Although several reports indicated that MCs concentrations in the sediments correlated to total *Microcystis* biomass in the sediments (Ihle et al., 2005), or intracellular MCs in the water (Mohamed et al., 2006), many factors have influence the variability of MCs in lake sediments. These factors included but not limited to, sedimentation of suspended particles (Wörmer et al., 2011), ability of adsorption of dissolved MCs from the water (Mohamed et al., 2006; Chen et al., 2008; Song et al., 2014), organic matter content and particle size fraction, as well as the hydrological parameters of lake water, such as precipitation, evaporation, water temperature, salinity, pH, mean water level and discharge flow (Song et al., 2015). Although MCs is likely present high amount in sediment, the mechanism of absorption or sedimentation of MCs on sediment as well as the interrelation of MCs from sediment to living organisms is poorly understood. Moreover, the toxicity of MCs in sediment on benthic communities is still unknown. Thus, future investigation and experimental studies intended to more fully understand the interrelation of MCs in lake sediment is recommended.

The implications of cyanobacterial toxins in food webs or the apparent contribution of cyanobacterial toxins in food webs with respect to living organisms and ecosystem health have been discussed previously in detail (Christoffersen, 1996; Preece et al., 2017). Obviously, understanding the dynamic of these toxins in aquatic compartments is essential to understanding the potential for trophic transfer of these toxins. Moreover, by understanding the role of these toxins in living organisms will allow researchers to understand the comparative toxicity of cyanotoxins and their effects on human.

3. Accumulation of microcystin in water column

The occurrence of cyanobacterial blooms associated with cyanotoxins has been reported throughout the world in surface waters, where hepatotoxic MCs are more commonly found in over 75% cyanobacterial blooms (Harke et al., 2016). Water column is the areas (aqueous phase) that first receive MCs from cyanobacteria. Data of MCs from field surveys have been reviewed in numerous papers (Falconer and Humpage, 2006; Messineo et al., 2009; Harke et al., 2016). A summary of cyanobacterial blooms, their prevalence and MCs recorded throughout the world are shown in Supplementary table S1. Literature reports generally agree that *Microcystis* are among the most common bloom-forming species in surface freshwaters. *Microcystis* blooms associated with MCs have been reported in 108 countries and territories, and MCs were found in 79 of these locations (Harke et al., 2016). MC content levels have been reported in surface waters varying from trace concentrations to several milligrams per liter. High MCs are often recorded in the summer period and immediately after the breakdown of a major bloom (Song et al., 2007). Recent evidence has shown that warmer conditions and climate changes have enhanced cyanobacterial bloom in water systems. This may result in increasing the frequency and levels of MCs in water column. For instance, one field laboratory study showed the MCs concentration in Lake Taihu was nearly 20 times higher than previous records (Song et al., 2007).

Water from some of the largest and most important freshwater resources on Earth are being contaminated with MCs including, but not limited to Lake Erie (USA, Canada), Lake Winnipeg (Canada), Lake Victoria (Kenya), and Lake Taihu, China (Davis and Gobler, 2016). Because of variations in extraction and detection methodologies, in concert with different starting materials (i.e., dried, wet samples, filtered), comparing concentrations of MCs among water bodies and between studies is challenging. Nevertheless, extremely high levels of MCs during *Microcystis* blooms have been reported worldwide. For example, MCs concentration reached 7300 $\mu g\,g^{-1}$ dry weight (dw) in China (Harke et al., 2016), 7100 $\mu g\,g^{-1}$ dw in Portugal (Vasconcelos et al., 1996). Very high concentrations of MCs in water (including intracellular and extracellular) have been reported up to 19.5 $mg\,l^{-1}$ in lake Suwa, Japan (Harke et al., 2016), 29.2 $mg\,l^{-1}$ in Lake Oubeira, Algeria (Nasri et al., 2004), or 36.5 $mg\,l^{-1}$ in lake Horowhenua, New Zealand (Wood et al., 2006) (Supplementary table S1).

Although a large number of studies have documented the occurrence of MCs in aquatic ecosystem, little is known about the influence of environmental factors on the bioaccumulation of MCs in water column. Water temperature is often considered the most important determinant of growth and metabolism of MCs in cyanobacteria (Xue et al., 2016; Preece et al., 2017). In fact, cyanobacteria bloom associated with MCs often occur during the warm summer season or when water temperatures are higher than usual in freshwater ecosystems (Pham et al., 2017). Thus, many studies have demonstrated that high water temperature was closely correlated with cyanobacterial biomass and cell bound MCs (Paldavičienė et al., 2015; Xue et al., 2016). Probably, water temperature is a critical factor influencing the toxic cyanobacterial blooms, and therefore indirectly correlated with the accumulation of MCs in water column. Although most freshwater cyanobacteria cannot survive for extended periods in marine and estuarine

environments, high salinity are thought to enhance toxins producing genera to break apart and release MCs into water column (Preece et al., 2017).

Cyanotoxins and their producers were reported mainly in surface water; the occurrence of toxins at different depth of the water column is limited (Agha et al., 2014). It is known that MCs and cyanobacteria cells are often retained on the surface water layer (often 0–1 m); however MCs could be mixed through the water column after cell lysis (Song et al., 2015). Xu et al. (2010) observed that *Microcystis* abundance at the bottom of water was sometimes higher than that of the surface water, especially before and after the water bloom season. This indicated that *Microcystis* colonies (cells) were distributed differently at different depths in the water column. In a study from three Turkish freshwater lakes, MCs were not found in the water column in Lake Sapanca, Turkish above 10 m, but several MCs variants with the concentration of 3.65 $\mu g\, l^{-1}$ were detected in filtered cyanobacterial samples from a 20 m depth. The highest content of MCs in Lake Sapanca was found between depths of 15 and 25 m (Albay et al., 2003). In a recent review, Catherine et al. (2013) stated that multiple benthic species of cyanobacteria have been reported to produce MCs and therefore could contribute to the total MCs burden in the aquatic ecosystem. The involvement of toxic population of benthic cyanobacteria in animal poisonings has increased markedly during the last decade. Therefore, future research should pay more attention to benthic cyanobacterial community in order to effectively control harmful algal bloom.

Episodes of cyanobacterial blooms associated with their toxins have recently been rather well documented in subtropical and temperate regions. However, studies on tropical toxic cyanobacterial blooms are sporadic (Mowe et al., 2015). In Vietnam, several investigations of toxic cyanobacteria and their toxins have been undertaken. Cybanobacterial blooms producing MCs up to 1116 $\mu g\, l^{-1}$ in cyanobacterial scum samples have been reported in the Nui Coc, Dau Tieng and Tri An reservoirs that have been using for drinking water and recreational activities, including fish farming and fishing (Duong et al., 2014; Dao et al., 2016; Pham et al., 2017). Although blooms of *Microcystis* spp. associated with MCs are common recorded in Vietnamese waters, only one study on bioaccumulation of cyanotoxin in aquatic animals has been currently conducted (Pham et al., 2017). Hence, during the period of cyanobacterial bloom with high MCs concentrations in the water, local people may suffer from toxic effects through drinking water, or by eating contaminated foods. Moreover, the presence of other cyanotoxins such as anatoxins, cylindrospermopsin, saxintoxins and their adverse effects are potential and that warrant further investigation.

4. Accumulation of microcystins in aquatic animals

Microcystins are known to generate adverse effects on aquatic species. The toxicity mechanism of MCs on tested animals has been verified in a number of studies including histological, biochemical and behavioral effects (Malbrouck and Kestemont, 2006; Pavagadhi and Balasubramanian, 2013; Chen et al., 2016; McLellan and Manderville, 2017). Exposed to MCs has resulted in decreasing growth and survival in tested organisms. In a recently reviewed by Pavagadhi and Balasubramanian (2013), significant changes on immunological indices, blood cells, and cellular enzymes activities in fish species upon exposure to purified MCs or cyanobacterial crude extract were highlighted. Chronic toxicity in fish exposed to toxic cyanobacteria has been demonstrated to promote osmoregulatory imbalance, increased volume of fluid in the gut, and inability to remove excess water. Extracts from cyanobacterial cells have resulted in inhibition ionic transport in gills of tilapia (*Oreochromis mossambicus*). Histological damages were also observed in liver, intestine, kidneys, heart, or in gills of fish exposed to MCs (Pavagadhi and Balasubramanian, 2013). Other adverse effects during early development include edema, reduced head size, curved body and tail, enlarged heart, increased heart rate, skeletal malformations and damaged hepatocytes (Malbrouck and Kestemont, 2006). In addition, recent reports have demonstrated that oxidative stress is also a toxicological consequence of the exposure to MCs in various aquatic animals (Chen et al., 2016; Elisabete et al., 2016). Indeed, exposed to MCs has resulted in an increase in lipid peroxidation, DNA damage, alteration of the antioxidant enzymes such as superoxide dismutase (SOD), peroxidase (POD) and catalase (CAT), and induction detoxification enzymes such as glutathione S-transferase (GST) and glutathione peroxidase (GPx) in different aquatic groups such as fish, bivalves and zooplankton (Chen et al., 2004; Amado and Monserrat, 2010; Ferrão-Filho and Kozlowsky-Suzuki, 2011). However, some aquatic species have a high tolerance to MCs that may be associated with responses of antioxidant and detoxification enzymes. One of the detoxification mechanisms of MCs involved GSTs that catalyze conjugation of MCs with glutathione (GSH). The conjugation of MC-GSH leads to reducing toxicity and accelerating excretion of MCs. Detoxification mechanisms are responsible for aquatic animals against toxicity or resistance to cyanobacterial toxins (Amado and Monserrat, 2010). Previous studies however have just focused on individual toxic model for toxicity screen. There is no report of toxic effects at population levels. Thus, more research on reproductive ability, development as well as threat to population or community levels is needed to improve our understanding of cyanotoxins toxicity on aquatic animals.

Despite these negative impacts, aquatic animals contact directly with toxic cyanobacteria regularly. Most aquatic organisms have the ability to accumulate MCs. An ubiquitous occurrence of MCs in aquatic animals was observed. In natural conditions, aquatic animals may expose simultaneously to MCs via two main route including consumption or/and drinking of toxic cyanobacterial cells and other organisms that have contaminated with cyanotoxins. This consumption is generally considered the primarily route of MC exposure. Therefore, exposure to higher toxic strains has resulted in greater MCs concentration in tested organisms. Another potential way is direct absorption of dissolved MCs from the surrounding water (Martins and Vasconcelos, 2009). The accumulation of MCs in aquatic animals has been reviewed in several papers (Martins and Vasconcelos, 2009; Ferrão-Filho and Kozlowsky-Suzuki, 2011; Preece et al., 2017). Based on literature data, the highest MCs concentration was found in zooplankton, reaching values over 1300 $\mu g\, g^{-1}$ dw and an average value of about 383 $\mu g\, g^{-1}$ dw ($n = 34$). MCs level reported in fish was often lower than for zooplankton (Fig. 3). Liver is a major target organ for MCs accumulation. However, concentrations of measured MCs in fish varied among the organs and species. For the zooplanktivore, the highest concentrations of MCs (874 $\mu g\, g^{-1}$ dw) in fish were found in the liver of *Osmerus eperlanus* (Ibelings et al., 2005). By contrast, considerable amounts of MCs have also been reported in gut of omnivorous fish that feed on either phytoplankton cells or animals (up to 390 $\mu g\, g^{-1}$ dw in gut of Nile tilapia *Oreochromis niloticus*) (Semyalo et al., 2010). Level of MCs accumulated in carnivorous fish was lower than in omnivorous and planktivorous, with a maximum of 51 $\mu g\, g^{-1}$ dw in the liver of perch (*Perca fluviatilis*) (Ibelings et al., 2005). Because they all burrow and filter-feeder, bivalves and gastropods were reported to accumulate high amounts of MCs. The maximum contents of MCs in bivalves and gastropods were 630 $\mu g\, g^{-1}$ dw and 436 $\mu g\, g^{-1}$ dw, respectively (Ferrão-Filho and Kozlowsky-Suzuki, 2011). Although not as common as MCs found in fish and bivalves, MCs has been detected in stomach of

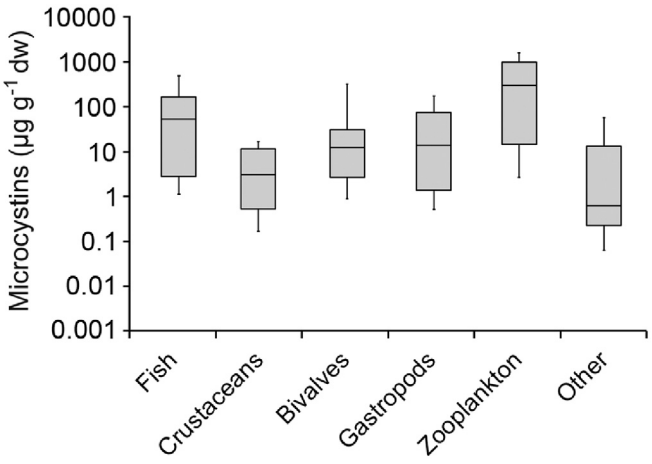


Fig. 3. Accumulation of microcystins (MCs) in different aquatic animal groups.

crustacean *Macrobrachium nipponensis* with a maximum concentration of 12.4 μg g^{-1} dw (Song et al., 2007).

Other aquatic animals such as turtles, amphibians and reptiles have been confirmed to contain MCs. Level of MCs ranging from 9.4–1193 μg g^{-1} dw have been detected in the liver, viscera and muscle tissues of two freshwater turtle species *Emys orbicularis* and *Mauremys leprosa* from Lake Oubeira (Algeria, Tunisia). Chen et al. (2009b) also reported MCs in liver and intestines of the Chinese soft-shell turtle *Pelodiscus sinensis* from Lake Taihu (China) with the highest level of 0.02 μg g^{-1} dw.

5. Accumulation of microcystins in plants

In animal cells, MCs require uptake via the bile acid transport system present in hepatocytes and cells lining the small intestine (McLellan and Manderville, 2017). However, MCs are generally not able to enter vegetable cell membranes (Ha and Pflugmacher, 2013; Machado et al., 2017). MCs may mainly accumulate directly via root adsorption of dissolved MCs, diffusion or be biotransformed by the enzymatic transformation of glutathione and cysteine into MC conjugates via soluble glutathione transferases, or GST in vegetable cells (Ha and Pflugmacher, 2013; Romero-Oliva et al., 2014; Machado et al., 2017). When exposed the emergent reed plant *Phragmites australis* to MCs, the main uptake route in the stem and rhizome has been observed (Corbel et al., 2014). Other uptake route may also occur by direct contact of leaves with surface water. One in vegetable cells, the same toxicity mechanism of MCs in vertebrate cells was observed (Fig. 4). That is the potent and specific inhibitors of PP1 and PP2A, and this inhibition accounts for their extreme toxicity of MCs in vegetable cells (Corbel et al., 2014). In addition, a number of studies observed that MCs have resulted in several perturbatory effects and induction of oxidative stress manifested by elevated ROS production and malondialdehyde (MDA) content on plant physiology (Ha and Pflugmacher, 2013; Romero-Oliva et al., 2015). Other studies reported that MCs have the potential to exert toxic effects on physiological processes or induce the growth inhibition of macrophytes (Romero-Oliva et al., 2015).

In aquatic ecosystem, macrophytes may directly contact dissolved MCs in water column. Recently, research on the uptake and effects of MCs on aquatic plants has increased (Romero-Oliva et al., 2014, 2015). The ability of MCs to accumulate in the tissues of different plants has been described previously, and it was recently reviewed by Corbel et al. (2014) and Machado et al. (2017). A number of studies have shown that MCs can be accumulated by many floating and submerged aquatic plants, such as *Ceratophyllum demersum*, *Elodea canadensis*, *Vesicularia dubyana*, and *P. australis* with the concentration up to 16.9 μg g^{-1} dw (Supplementary table S2). The accumulation of MCs in plants seems to depend not only on the dose and kind of toxin, the route of exposure, target organs, the duration of exposure, but also on the target tissues and specific species. A higher rate of absorption in the root system has frequently been observed (Saqrane et al., 2009). Xiao et al. (2009) reported that water chestnut (*Trapa natans*) from Lake Tai accumulated MCs at highest level up to 7.02 ng g^{-1} dw. In addition, Mitrovic et al. (2005) observed that the duckweed *Lemna minor* can accumulate MCs up to a concentration of 0.3 ng mg^{-1} wet weight (ww), after 5d of exposure to MCs at 20 μg l^{-1} with an accumulation rate of 58 ng g^{-1} d^{-1}. Recently, time dependent uptake, bioaccumulation and biotransformation of cell free crude extract MCs were reported in the hornwort *C. demersum*, the large-flowered waterweed *Egeria densa* and the waterthyme *Hydrilla verticillata*. The highest MCs bioaccumulation capacity was observed in *E. densa* followed by *C. demersum* and *H. verticillata* (Romero-Oliva et al., 2015). Bioconcentration factors were up to 165 in *Eichhornia crassipes* living in the Lake Amatitlán (Guatemala) contaminated with MCs (Romero-Oliva et al., 2014).

Despite adverse effects of MCs on aquatic plants, these plants

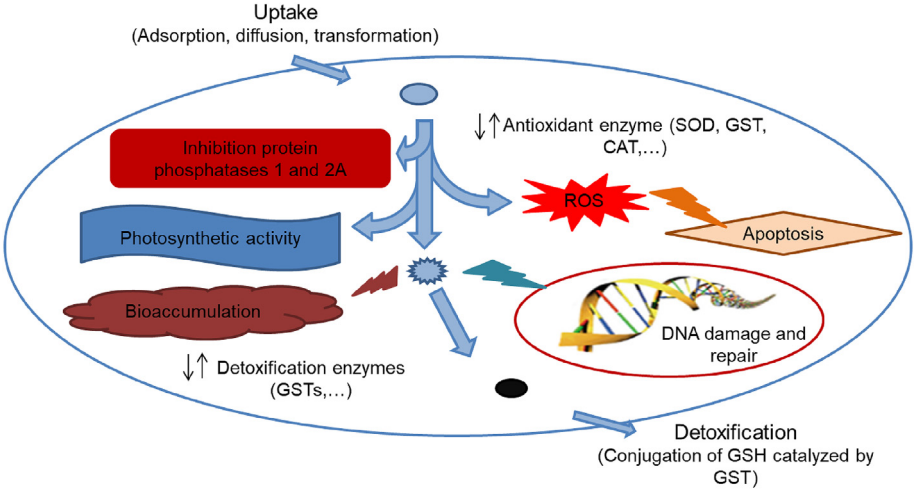


Fig. 4. Toxicity mechanism of microcystins (MCs) in plant tissues.

may adapt and develop a resistance to these toxins through biotransformation processes. MCs accumulated in aquatic organisms were mainly detoxified via conjugation of GSH catalyzed by GST during phase II biotransformation (Ha and Pflugmacher, 2013). Many studies have reported that MCs stimulated antioxidant and detoxification enzymes in aquatic plants, indicating that MCs trigger the activation of detoxification system in aquatic plants. In a laboratory experiment, Romero-Oliva et al. (2015) exposed several macrophytes including hornwort *C. demersum*, the large-flowered waterweed *E. densa* and the waterthyme *H. verticillata* to cell free crude extract containing MCs. The results showed that tGSH concentrations in all exposed macrophytes were enhanced by MCs, suggesting that detoxification pathway for MCs activates in these plants.

It is known that terrestrial plants, including many crop plants, do not directly contact MCs and cyanobacterial blooms. However, these plants could be exposed to cyanobacterial toxins via irrigation water contaminated with cyanotoxins (Peuthert et al., 2007; Levizou et al., 2017). MCs dissolved in irrigation water could be absorbed by roots and translocated from roots to shoots in the seedlings of agricultural plants (Peuthert et al., 2007). When exposed lettuce (*Lactuca sativa* L.) at different stage including (seed, 2 leaves and 4 leaves) to MCs-rich water originating from the Karla Reservoir, central Greece, Levizou et al. (2017) reported that highest MC concentration was found in the seed stage. In other stage, highest MC levels were often found in the root. The effects caused by MCs on terrestrial plants vary from inhibition to stimulation the seedling development, and include reduction of PP1 and PP2A, oxidative stress, decreased photosynthetic activity, DNA damage and repair and even cell apoptosis (Fig. 4) (Corbel et al., 2014; Bittencourt-Oliveira et al., 2016; Machado et al., 2017). Inhibition of growth and development in *Brassica chinensis* and *Brassica napus* grown under various concentrations of MCs (from 0.008 to 4 mg l^{-1}) has been reported. Besides, the activities of SOD, POD and CAT were induced (Xue et al., 2010). Multiple negative effects of MCs including reduction in growth, productivity, activity of photosystem II and increase in the accumulation of nutrients in the plant roots of *Triticum durum*, Zea mays, *Pisum sativum* and *Lens esculenta cultivars* have been observed (Saqrane et al., 2009). Indeed, many crop plants with MCs concentrations that exceed the recommended tolerable limits of the WHO have been documented (Corbel et al., 2014). Therefore, agricultural crops irrigated with water that contains MCs have posed potential risks to the health of both farm animals and humans.

In lentic waters where cyanobacterial blooms frequently occur, macrophytes may be exposed continuously to fluctuating concentrations of MCs. The accumulation and detoxification capacities during prolonged exposure are still unknown. In addition, understanding the factors affecting MCs accumulation as well as detoxification in macrophytes is still challenging. A better understanding of the plants' uptake and subsequent accumulation and biotransformation abilities could elucidate their role in water treatment and environmental management.

6. Accumulation of microcystins in sediment

Because of the difficulty in extracting total toxins from sediments, analysis of MCs in aquatic environment has been limited to determining the MC content in water (Song et al., 2015). However, sediments collected from lakes and benthic marine ecosystems in which no benthic cyanobacteria was observed were reported to be contaminated with MCs (Chen et al., 2008; Umehara et al., 2017). Previous studies stated that MCs in sediment were highly variable on the temporal and spatial scales (Chen et al., 2008; Gurbuz et al., 2016; Umehara et al., 2017). However, the highest MC content in sediment usually reflects the MCs in water and usually associated with bloom seasons (Gurbuz et al., 2016). The distribution and annual variations of MCs in sediments of Lake Taihu, China were reported by Chen et al. (2008). These authors found that MCs were mainly distributed on the surface of sediment, with concentrations ranging between 20.4 and 168.1 ng g^{-1}, and MC contents decreasing with increasing sediment depth. Although MCs were weakly retained in the natural sediments, high levels of MCs in the lake sediment samples (especially those containing high concentrations of clay) have been documented (Chen et al., 2006). In a recent study, Gurbuz et al. (2016) reported that MCs were present in samples sediment with concentrations from 7–17.6 μg g^{-1} dw, even when no MCs was recorded in water. In addition, toxic cyanobacteria with their toxin can travel from freshwater areas into the sea. Indeed, MCs from a freshwater reservoir (Isahaya Bay, Japan) have been found to be discharged and remained in the surface sediments, and then accumulated in various areas of benthic marine ecosystems (Ariake Bay, Japan) (Umehara et al., 2017). Therefore, this should be taken into consideration when performing investigations of the fate of cyanotoxins in the aquatic environments.

Basin sediment has been regarded as a potent biodegraders as they have the capacity to conduct absorption or biodegradation of MCs into less toxic byproducts compounds through the sediment's bacterial community. Wörmer et al. (2011) showed the great importance of sedimentation processes in the fate of MCs in freshwaters with an amount of toxin associated to settling particles to be in the range of mg d^{-1} m^{-2}. But other studies reported that MCs have been shown to absorb only weakly on lake sediment and usually no more than 20% of toxins can be adsorbed (Chen et al., 2008). In laboratory experiments, Song et al. (2014) found that biodegradation was shown to be the main process in benthic phase. Numerous microorganisms involved in MC degradation have been recorded, such as *Pseudomonas aeruginosa, Methylosinus* and *Sphingomonas*. These bacteria communities are always prevalent in natural waters and sediments (Zhao et al., 2017). The contribution of sediments to the involvement of MCs in the water is important for understanding the fate of MCs in aquatic systems, which may lead to better management strategies. Furthermore, this emphasizes the potentially useful abilities of sediments in the biodegradation of MCs, if they were to be used in, e.g., water treatment facilities.

In addition, lake sediment has been known for its role in the continuation of cyanobacteria populations and conservation of "seed banks" for the following year. It play an important role in the overwintering populations of cyanobacteria that act as potential inocula for summer blooms by hosting akinetes (Cirés et al., 2013). The germination of akinetes from the surface sediment is initial for next cyanobacterial bloom scenarios. Thus, lake bed sediments might serve not only as an absorbent for dissolve MCs, but also as an incubation chamber for vegetative cells. Latour et al. (2007) reported the presence of high concentrations of *Microcystis* colonies at the sediment surface (250 colonies ml^{-1} sediment) and also at depths of 25–35 cm (2300 colonies ml^{-1} sediment) and 70 cm (600 colonies ml^{-1} sediment) in Grangent Reservoir, France. Thus, understanding the vital role of lake sediment in life cycle of cyanobacteria is important to control cyanobacterial blooms as well as monitor MCs content and cyanobacterial community in benthic phase.

7. Future directions

The increased incidence of MCs accumulation in aquatic ecosystem worldwide poses potential health risks, particularly in

developing countries, where drinking water and food still depend heavily on wild stocks and nature. Therefore, advanced approaches or new technology development is needed to control the harmful cyanobacterial blooms. To minimize the potential of MCs accumulation in aquatic ecosystems, it is better to prevent cyanobacterial blooms in water environment. To mitigate eutrophication and prevent cyanobacterial blooms, nutrient control is a fundamental process. Nitrogen and phosphorus play the most important role in the eutrophication of aquatic ecosystems. Therefore, it is critical to understanding their flow pathways in aquatic environment. It is not only provides a basis knowledge to identify possible pollution sources but also a means to develop new strategies to treat eutrophication and cyanobacterial blooms.

An ubiquitous occurrence of MCs in aquatic ecosystem was observed. However, there remain knowledge gaps concerning the future of MCs in sediments in terms of speciation, persistence, mode of transfer and impact on benthic life. Besides, there is no information on MCs toxicity and accumulation in benthic community such as nematode and benthic diatom. Therefore, future studies are needed, focusing on the dynamics of MCs between environments, toxicity mechanism especially in benthic communities. Notably, cyanotoxins in lakes, for example, may move downstream, eventually contaminating the sea and groundwater. In addition, bioaccumulation of MCs in toxicological experiments has been carried out only for the most common analogs. This may underestimate the risk of cyanotoxins poisoning. Further research is needed on possible additive, synergistic or antagonistic effects to multiple classes of cyanobacterial toxins as well as other bioactive metabolites.

The interdisciplinary studies between toxicology, biochemistry, and ecology may be a key and strategic approach to control bioaccumulation of cyanotoxins and reduce human health risk. Mitigate, prevent and control occurrence of toxic cyanobacteria is a current global challenge. Much of the current research on MCs bioaccumulation is focused on the case reports and toxic mechanisms in individual species. Hence, future scientific research needs to elucidate the complex transfer pathway of MCs at community levels. Such new knowledge can provide us with the requisite information to control MCs contamination in food webs. To recommend a more standardized and systematic approach to bioaccumulation of cyanotoxins in aquatic ecosystem, a comprehensive surveillance of environmental waters, aquatic products as well as sea food across each continent is also required. Development and implementation of specific guidelines for the collection, extraction and analysis of cyanotoxins in aquatic environment samples is also essential to obtain reliable and comparable results. Despite the current availability of data on the cyanobacterial toxicity and cyanotoxin accumulation in various aquatic organisms and crop plants, further investigations are needed in order to elucidate the fate of MCs as well as their mode transfer pathway between aquatic compartments.

In the perspective that prevention is better than cure, the education of local communities about the toxicity of cyanotoxins is essential. Consumers should be made aware to the serious consequences related to using food contaminated with cyanotoxins. Promote innovation and research on new effective techniques for detoxification of cyanotoxins from foods is fundamental in prevention and control of toxic effects.

8. Concluding remarks

This review article has summarized the research data available currently to the scientific community pertaining to the accumulation of MCs in aquatic systems, with specific focus on their distribution and interrelation in different aquatic compartments. MCs are ubiquitous in aquatic environment. Water column is the most contaminated with MCs and serves as an intermediate transmission substation. High levels of MCs in water have been directly distributed to different environmental compartments such as sediment, animals, aquatic and terrestrial plants in the aquatic ecosystem. Therefore, biomonitoring of MCs in water could serve to effectively manage these aquatic compartments and design contingency plans to mitigate their toxicity.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jenvman.2018.01.077.

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