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Review:

Toxicity of Microcystins on Human, Animal and Aquatic life

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Abstract

Microcystins (MCs) are a group of biologically active monocyclic hepatopancreatic peptides produced by some bloom-forming cyanobacteria in water. Toxic cyanobacterial blooms act as hepatotoxic, neurotoxic, cytotoxic in human and animal following long term ingestion of contaminated water. Plants, vegetables and food crops irrigated with microcystins contaminated water are negatively affected by MCs. Temperature light and high concentrations of nitrogen and phosphorus exposure are the primary three environmental factors that promote the formation of cyanobacterial blooms in surface water. MCs have been accumulated in plants, various aquatic organisms and animals until reach the top food chain. Therefore, high level of toxic cyanobacterial blooms in surface water has become an increasing environmental problem all over the world. Many countries in the world suffer from the problem of intensive cyanobacterial blooms in surface water. Hence the necessity for regular monitoring of the organic wastes discharge to the surface water should be highlighted and educating people about the dangers of microcystins on water hygiene standards as well as on aquatic, animal and human life.

Keywords: *cyanobacteria, toxicity, animal, surface water, organic wastes.*

1. Introduction

Microcystins (MCs) are a group of monocyclic hepatotoxic peptides, which are produced by some bloom-forming cyanobacteria in water, also they are known as a class of potent liver/hepatopancreatic toxins produced by several species of freshwater cyanobacteria and they are well known for their toxic effects on aquatic organisms and humans (Juliette et al., 2009).

MCs promote tumors through inhibiting protein phosphatases (Ren et al., 2017). The inhibition of protein phosphatase leads to phosphorylation causing various cellular responses such as reduced DNA repair, apoptosis and tumor promotion (Buratti et al., 2017), moreover MC-LR is a common cancer promoter in human (IARC, 2010, Žegura, 2016). Additionally they cause apoptosis, hemorrhage, necrosis, and inflammation of hepatocellular carcinoma due to the inhibition of protein phosphatases in higher organisms (Dittmann et al., 2006).

Microcystins are toxic compounds released from several cyanobacteria such as Microcystis, Anabaena, Oscillatoria and Nostoc (Pendleton et al., 2001). Cyanobacteria produce toxins at all stages of growth and these toxins generally remain in the cell, known as intracellular toxin, until age or stress causes them to release the toxin into the surrounding water in which it becomes extracellular toxin (Svrcek & Smith, 2004). After release of MCs in water, they have half-life of 4-14 days in surface water depending on the content of natural organic matter, the degree of sun light and presence of bacteria (Ministry of Health, 2017).

More than 100 different MCs variants, posing a great threat to animals and humans, due to their potential

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carcinogenicity had been identified. Microcystins and anatoxin are the most common toxins produced by cyanobacteria, threatening human health through the liver damage and nervous system, respectively (Khomutovska et al., 2020).

High frequency of cyanobacterial blooms poses a threat to human and animal health in lakes, reservoirs and oceans throughout the world (Sehnal et al., 2019). MCs are produced by several genera of cyanobacteria including Microcystis sp., Oscillatoria sp., Nostoc sp., Anabaena sp. and Anabaenopsis sp. and they are called hepatotoxic peptides which are found in freshwater bodies and desert environments (Buratti et al., 2017), and they are the most harmful cyanotoxins present in water bodies (Codd et al., 2016, Mantzouki et al., 2016).

The cyanobacterial blooms can alter the water quality and cause several problems such as fish kill, deterioration of recreational value, clogging of filters, existence of musty odor for water supply systems, interference with coagulation and flocculation processes, and passage into distribution systems (Dugan and Williams, 2006). In addition they impair the water uses for several purposes (Amado and Monserrat, 2010).

Furthermore, the cyanobacterial blooms affect the water quality by changing transparency, pH and biodiversity (Blahova´ et al., 2008), beside the toxin production, which is toxic to fishes, aquatic invertebrates, domestic animals and human (Zhang et al., 2009).

Microcystins were detected in different water sources all over the world. Mohamed (2016) found that MCs concentration in drinking water was 0.05–3.8 μg/L. While Dajun et al., (2013) in China found that MCs concentration were 1.846 μg/L in river and 2.298 μg/L in pond.

Human can be exposed to the toxic effect of MCs through consumption of contaminated water (Brooks et al., 2016), or ingestion of contaminated food (fish, crustacean, algal dietary supplement or animals and birds previously consumed contaminated water) (Lee et al., 2017a, Qian et al., 2017).

Due to the health hazard caused by exposure to microcystins, the World Health Organization has set a provisional guideline of 1 μg/L MCs in human's drinking water (Chorus & Bartram, 1999) and the maximum density limit of cyanobacteria in water supply reservoirs is 20.000 cells/ml (Brazil, 2011).

Conventional water treatment methods including coagulation, flocculation, sedimentation, and filtration are ineffective in removing MCs, moreover, cause further water contamination through release of intracellular MCs (Newcombe and Nicholson, 2004). Therefore, the health problem due to exposure to MCs should be highlighted.

2. Microcystins in different water sources

Blue green algae are very common in aquatic ecosystems especially in tropical areas where high temperatures and nutrient abundance promote their growth (Buratti et al., 2017). These conditions lead to eutrophication of the aquatic systems leading to unmeasured growth of phytoplankton; a phenomenon known as "bloom" (O'Neil et al., 2012). Cyanobacterial toxins are produced intracellularly and are commonly recorded to occur in natural water bodies worldwide (Funari and Testai, 2008).

These toxins get released into the water bodies either by natural method through cell lyses or artificial induction of cell lyses caused by treatment processes (Pietsch et al., 2002). The harmful cyanobacterial blooms in natural water have become an increasing environmental problem all over the world due to increasing the discharge of wastewater containing nitrogen and phosphorus to rivers and lakes (Haider et al., 2003).

Toxic cyanobacterial blooms are dominant in Eutrophic lakes, ponds, lagoons, streams and reservoirs worldwide (Howard et al., 2017), mainly in summer in temperate regions and at different points in time throughout the year in tropical and subtropical areas of Australia, South America and China (Dörr et al., 2010).

2.1- River water

Mohamed (2016) revealed that, in Egypt, MCs were detected in the water source of some drinking water treatment plants at concentrations ranging from 0.7 to 341 μg /L. Therefore Egypt has adopted the WHO guideline limit of 1 μg /L and tolerable daily intake (TDI) of 0.04 μg / kg body weight (Kuiper-Goodman et al., 1999).

Mohamed and Carmichael, (2000) studied the seasonal variation in microcystin levels of River Nile water at Sohag City, Egypt and revealed that microcystin concentration in cell-free water correlated significantly with that measured within the cells, with maximum values being recorded in September (0.4-0.78 μg/L). Microcystin levels in the finished drinking water were low (56.1- 87.1 ng/L) and were detected only in May and June.

Zakaria et al., (2015) performed a study to investigate the occurrence of cyanobacteria and their microcystin (MC) toxins in the Nile River source water of Damietta water treatment plant (WTP) during warm months (April–September, 2013). The lowest concentration of intracellular (1.3 µg/L) was obtained in April while the highest concentration (3.3 µg/L) was in August and the extracellular MCs were also detected at high concentrations (1.6–4.5 µg/L).

Fedekar et al., (2015) performed a study to evaluate the concentration of microcystin-LR in the drinking water supply (Ismailia Canal) and treated drinking water at Port Said Governorate, Egypt. Their results revealed that the concentrations of microcystin-LR were (12.28µg/L) during December and (9.08µg/L) August.

A significant regional difference in the release characteristics of MCs in water and the peak time in some regions also vary (Qing et al., 2019). MC-LR was detected in 44% of water bodies at a concentration 0.1 - 0.6 µg/L in southern Manitoba, Canada (Davis, 1998). Some studies in Bangladesh showed that microcystins present at toxic level of more than 10 µg/L in almost twenty drinking water resources (Welker et al. 2004).

Microcystins concentration was 2.47 µg/L in chlorinated drinking water when detected by Zamyadi et al., (2012). In September 2013, Carroll Township, Ohio was the first public water utility in the United States to release a 'do not drink' advisory because of cyanotoxin breakthrough (He et al., 2016). The utility detected 1.4 and 3.6 µg/L of microcystin equivalents in their treated water, which exceeds the State of Ohio's and the World Health Organization's 1 µg/L microcystin equivalent threshold for drinking water (He et al., 2016).

Masango et al., (2010) reported an increase of microcystins from an average of 49.41 µg /L in February during summer blooming of the cyanobacteria, to 103.16 µg /L in June in the dam water found in the Kruger National Park (South Africa). This increase in microcystin concentration was as a result of the dying-off of cyanobacterial cells in winter.

The MC-LR concentration in South Korea was 1–7.2 µg/L in samples collected from the Han River in August 2016 (Lee and Son, 2019). Moreover, microcyctin were estimated at low level in some water bodies including the Klamath River and its reservoirs (Claifornia) where the detected level was 0.32 µg/L (Kann, 2007).

2.2- Irrigation water

Many countries all over the world suffer from the problem of intensive cyanobacterial blooms in surface water (Pinho et al., 2003). MC-LR has been detected in surface water and included in surface water environmental quality standards and drinking water hygiene standards in different countries to ensure the drinking water safety (Guobin et al., 2020). Toxic cyanobacterial blooms were detected in fresh water (Zervou et al., 2016) and brackish water (Spoof and Catherine, 2017).

MCs concentration in whole water of Lake Taihu (China) was 23.26 µg/L which was higher than the maximum permissible limit (1 µg/L) recommended by WHO (Su et al., 2018).

According to a study performed by Duong et al., (2013) the concentration of MCs in Hoan Kiem Lake in Vietnam reached 46.0 µg/L.

Since 2000, the Brazilian Health Ministry incorporated cyanobacteria density and cyanotoxin concentration testing parameters that must be monitored in reservoirs utilized for drinking water. The maximum density limit (20.000 cells/ml) of cyanobacteria in water supply reservoirs and the concentration limits of MCs for drinking water is 1.0 mg/L (Brazil, 2011).

The presence and increase of cyanobacterial cell concentration not necessarily correlated with an increase of the toxin concentration (Turner et al., 2018). Another study revealed that there is strong correlation between cyanobacterial cell density and MCs concentration (Abu Affan et al., 2015).

A study done by Vasconcelos et al., (2010) revealed the occurrence of MCs in lakes and reservoirs in central Mexico and the concentrations ranged from 4.9 to 78.0 µg/L.

2.3- Wastewater

The total microcystins concentration in Lake Taihu (Jiangsu, China) was 23.26 µg/ L (Su et al., 2018). The concentration of total MCs in the water samples collected and examined by Dajun et al., (2013), Sagir et al., (2014) and Hélène et al., (2019) from Huai River Basin of (China), eutrophic pond (Bangladesh) and Pigeard pond

(France) were 0.597 ± 0.960 µg/L, 4.0 µg/ L and 34.4 µg/L, respectively.

Sabah et al., (2010) studied the phytoplankton communities of two ponds (facultative and maturation) of the wastewater treatment plant of El-Sadat city (Egypt) with particular importance given to cyanobacteria. During the study period which was from December 2005- March 2007, cyanobacteria were frequently dominant in these ponds ranging from 2.2- 97.8 % of total phytoplankton density and the main species was Oscillatoria spp.

Cyanobacteria are particularly adapted for survival in wastewater treatment facilities due to the long water residence times and eutrophic state of waste water treatment facilities stabilization ponds.

The presence of cyanobacteria in wastewater treatment ponds is not necessarily indicative of the presence of cyanotoxins because the potential for toxicity is strain dependent (Christiansen et al., 2008; Srivastava et al., 2016). Even if the requisite toxin biosynthesis genes are present, toxin production can be temporarily suspended due to unfavorable environmental conditions (Wood et al., 2011). General factors associated with the regulation of cyanotoxin production include light intensity and exposure, nutrient concentrations, water temperature and stratification, and the production of allelochemicals by competing organisms (Neilan et al., 2013).

3. Factors affecting concentration of MCs in different water sources

Environmental, metrological and hydrological parameters have been used to model cyanobacterial concentration (Rigosi et al., 2015). Temperature, high concentrations of nitrogen and phosphorus and light exposure are the primary three environmental factors that promote the formation of cyanobacterial blooms (Merel et al., 2013). Under favorable conditions including warm temperatures, sunlight irradiance and increased nutrient concentrations, cyanobacterial cells can multiply and form harmful cyanobacteria blooms in lakes and rivers (Huber et al., 2012).

MCs can accommodate wide range of temperature and salinity and can occasionally occur in rocks and soils (Svrcek & Smith, 2004). Cyanobacterial blooms dominate aquatic environments under warmer and nutrient-rich conditions because they have physiological and ecological adaptation (Carey et al., 2012). Cyanobacteria exhibit rapid growth and multiplication under favorable environmental conditions such as temperature, which typically 15 to 30 oC and pH typically 6 to 9, salinity and light leading to formation of blooms (Cuypers et al., 2011; Merel et al., 2013). Moreover, some environmental conditions can stimulate cyanobacterial growth causing a dense accumulation of cyanobacterial cells at the water body surface and is commonly called as a cyanobacterial bloom.

Generally, the rapid increase of human population and consequent intensification of agricultural and industrial activities along with deficient water management have led to the enhancement of eutrophication in superficial freshwater bodies used for domestic purposes and as drinking water sources (De Figueiredo et al., 2004).

Similarly, cell growth rate, competition, predation and water flow stimulate the biosynthesis of microcystins and other secondary metabolites affect the microcystins concentration in water sources (Merel et al., 2013).

4. Exposure routes to MCs

There are two main methods for exposure to cyanotoxins: direct method through consumption of contaminated water and indirect method through the consumption of foods such as fish, crustaceans, molluscs and plants (Poste et al., 2011; Papadimitriou et al., 2012). Moreover, human can be exposed to MCs through diverse routes as dermal, respiratory, body contact (during recreational activities), hemodialysis (Ibelings et al., 2016, He et al., 2016).

Fishes are exposed to MCs either actively, during feeding (Fischer et al., 2000), or passively through the gills (Malbrouck and Kestemont, 2006) and because they are located at the top of the feeding chain they implement a great threat to the human (Magalhaees et al., 2001). It was proven that 80% of the daily consumed MCs came from ingestion of contaminated water and the remaining 20% came from consumption of contaminated food and inhalation (Dietrich and Hoeger, 2005). Drinking contaminated water

Contamination of drinking water with MCs is considered as immediate threat to the human (Brooks et al., 2016; Lee et al., 2017b), in China, high rate from hepatocellular carcinoma was observed in human consuming drinking water with toxic cyanobacteria especially microcystis (Ueno et al., 1996), consumption of drinking water containing MCs caused illness and death of livestock, pets and wildlife (Svircev et al., 2017).

4.1- Consumption of sea food

Free microcystin concentrations reported have ranged from 0.42 µg/kg in crabs (De Pace et al., 2014) to 337.3 µg/kg in fish (Magalhaees et al., 2001). The transfer of food and persistence of these toxins have resulted in intoxication of aquatic biota such as fish, mussels, crustaceans (Pham and Utsumi, 2018) and humans (Massey et al., 2018). Also, the depuration experiments showed constant levels of MCs after 2 weeks, and elimination, just after 60 days (Smith and Haney, 2006).

Several studies have been detected high concentration of cyanotoxins in fish tissues from systems with high concentrations in water (Amrani et al., 2014). Microcystins accumulation in fishes is affected by several factors including the concentration of the specific toxin(s) in the environment in combination with the period of exposure and fish metabolic processes (Gurbuz et al., 2016). In fish, the concentration of cyanotoxins is reported to be higher in liver, intestine and kidney relative to that in mussles muscle.

4.2- Intravenous exposure

Human can be exposed to microcystins, specifically microcystin-YR and -LR intravenously during dialysis and this exposure route is a major cause of death during dialysis process so that the toxins were detected in the patient's blood and liver (Azevedo et al., 2002).

4.3- Recreational activities

Exposure to microcystins through recreational activities such as swimming, boating, skin contact, swallowing lake water or breathing water spray is more common in children than adult (Minnesota Department of Health). Contact of MCs with the body result in eye, ear and skin irritation, rashes and other allergic reactions (Pilotto et al., 2004).

5. Mechanism of action of Microcystins

The main route of microcystins action in cells is inhibition of the activity of protein phosphatase 1 or 2A (Toivola et al., 1994) resulting in cell proliferation and cancer or an apoptotic process and cell death (Toivola and Eriksson, 1999). Mitochondria as main energetic centers play an important role in apoptosis through targeting β-subunit of ATP synthase (Zaccaroni and Scaravelli, 2007) and hyper phosphorylation leading to acute liver failure (Falconer, 2008), intrahepatic hemorrhage (Kaasalainen et al., 2009), development of cancer (Valério et al., 2016), and cell death in high dose exposure (Toivola and Eriksson, 1999) rounding of cell, cell separation from each other, cell blebbing, cell fragmentation, glycogen depletion and vacuolization can also be produced from MCs exposure (Drobac et al., 2016).

Two other mechanisms of microcystins toxicity are oxidative stress formation (lipid peroxidation induction, reactive oxygen species production, reduced glutathione content, etc.) and cytokine production (Gaudin et al., 2008; Puerto et al., 2010).

Toxic cyanobacterial blooms act as hepatotoxic (microcystins), neurotoxic (Hu et al., 2016), cytotoxic or skin irritants (dermatotoxic) (Lian et al., 2014; Zamyadi et al., 2015), “Swimmer’s itch” is a severe contact dermatitis which occurs after swimming in marine waters that contain specific cyanobacterial blooms (e.g., Lyngbia majuscula). Also, they cause gastrointestinal troubles as well as respiratory disturbances (Buratti et al., 2017).

Because adsorption of MCs through the respiratory route is possible and can result in damage to nasal epithelium at low doses (Benson et al., 2005) and death at high intra-tracheal exposures (Ito et al., 2001). It is difficult to quantify the health risks caused by exposure to microcystins because the actual exposure and the resulting effects have not been conclusively determined, especially in relation to humans (Chen et al., 2009). They cause diarrhea, dysentery, hepatitis and liver cancer as reported by Lu and Lin, (2001).

6. Health effects of microcystins

Harmful cyanobacterial blooms can have negative appealing and economic impacts, but the primary cause for their severity is that they often produce potent hepatotoxins and neurotoxins which have been linked to severe illness and even death in aquatic life, wild animals, livestock and even human beings (Cai et al., 2019). Exposure to toxic cyanobacterial blooms may cause hepatotoxic effects (Gupta and Guha 2006), kidney damage (Fischer and Dietrich, 2000), per-acute neurotoxicosis, gastrointestinal disturbances as well as respiratory and allergic reactions (Buratti et al., 2017).

6.1- Toxicity of MCs on human

Microcystins cause death in human when exposed to them through hemodialysis (Svircev et al., 2017). The extreme cases of human poisonings were manifested in Caruaru, Brazil in 1996 where 116 of 131 patients showed visual disturbances, nausea, vomiting and muscle weakness following routine dialysis then developed acute liver failure and more than 60 hemodialysis patients died from these symptoms what is now called “Caruaru Syndrome” (Catherine et al., 2016).

MCs were identified for the first time in the serum (average 0.228 ng MC-LR eq/ml) of a chronically exposed human population (fishermen at Lake Chaohu, China) together with indication of hepatocellular damage. During the past decades, the lake has witnessed a steady increase in eutrophication, characteristic of a regular occurrence of cyanobacterial surface blooms (mainly composed of Microcystis spp. and Anabaena spp.) in the warm seasons of each year (Deng, 2004).

It was revealed by epidemiological investigations that MCs may be the cause of appearance of high incidence of liver cancer in populations dependent upon MC-contaminated drinking water in China (Ueno et al., 1996), Serbia (Svircev et al., 2009), Florida of the United States (Fleming et al., 2002) and colorectal cancer in China and Taiwan (Zhou et al., 2002) also in USA and Australia (Zhou et al., 2016). The exposures to MCs are underestimated due to difficult and expensive toxin detection methods (Humbert, 2010) and complex factors that also cause disease (Ahmed et al., 2007).

6.2- Toxicity of MCs on animals

The first suspected animal poisoning case in New Zealand caused by consumption of toxic cyanobacteria in farm ponds in Waipukurau, Masterton, and in the Bay of Islands (North Island) (Hint, 1966).

Mortalities of wild life and cattle have been linked to MCs poisoning (Briand et al., 2003). The accidental ingestion of cyanobacterial toxins resulted in abdominal pain, nausea and fever followed by dyspnea and respiratory distress 3 days later (Giannuzzi et al., 2011).

Cattle having survived acute intoxication may develop hepatic photosensitization. Secondary (hepatogenous) photosensitization is the most common type of photosensitivity seen in animals and occurs due to liver or bile duct damage, most often as a result of ingestion of hepatotoxic plants. This condition is characterized by clearly demarcated sunburn like lesions that are localized in hairless areas of skin. The nose, lips, udder and ears are the most commonly affected areas (Tim et al., 2012).

Deaths of domestic and wild animals were studied by Willen et al., (2011) around Rift Valley in Kenya and traces of microcystins produced by Microcystis aeruginosa where reported as the dominant species. The toxins were found to exceed 1 µg/L levels. Also, microcystins are reported to be globally toxic in domestic and wild animals, furthermore they cause pet deaths in both more and less economically developed nations (Qin et al., 2010).

6.3- Toxicity of MCs on aquatic organisms

Hepatotoxins have been detected in benthic cyanobacteria worldwide (Fetscher et al., 2015). Benthic cyanobacteria are a part of biofilms growing on the surface of the sediment in water bodies. They are organized in mates or clusters forming, with the help of other autotrophic microbes, the photosynthetic layer of epilithic biofilms. Cyanotoxins in surface water is of great importance in United States and other parts of the world cause high mortalities in fishes, shellfishes and wild and domestic animals as well as human sickness such as nervous system damage or liver injury, gastroenteritis problems, and in extreme cases, death (Mantzouki et al., 2016).

Zervou et al., (2016) reported that MCs have been accumulated in various aquatic organisms including fish, shellfish and zooplankton, which are further consumed by human. Cyanobacteria can be found almost everywhere in terrestrial and aquatic environments, even in Antarctic lakes and hot springs (Durai et al. 2015).

There are a few studies examining microcystins content in the freshwater species Cyprinus carpio (Fischer and Dietrich, 2000), Tilapia rendalli (Magalhaees et al., 2001), Oreochromis niloticus (Deblois et al., 2011), some phytoplanktivorous fish (silver carp, Hypophthalmichthys molitrix) (Chen et al., 2007) and omnivorous fish such as Carassius gibelio (Kagalou et al., 2008). The mutagenic effects of MCs in fish were reported by (Moreno et al., 2009).

Microcystins cause hepatotoxicity, oxidative stress, osmoregulation imbalance and impairments in the gonadal development in fish (Hou et al., 2017Paulino et al., 2017;). MC-LR is suspected to induce alteration of the immune response especially in fishes in which most of the studies addressing immune-toxic effects have been done (Lone et al., 2016). For example, medaka fish affected with MC-LR show change in immune response and induced sustained pathological changes in the GIT, liver, and other organs (Djediat et al., 2010).

Conclusion

Microcystins contamination, due to cyanobacterial bloom, in different water sources (River, Irrigation and waste water) is considered one of the public health concerns worldwide due to its common hepatotoxicity and genotoxicity on human, animal and aquatic life. Therefore, great attention should be paid to the contamination of water bodies with organic contaminants. There is a need to draw up active water safety policies on MCs and their implementation be ensured and abide.

Authors' contribution

Concept and idea: Hosnia S. Abdel-Mohsein, Manal A. M. Mahmoud and Zakaria M. Zaky. Web research: Wafaa Kh. Kelini Draft writing: Wafaa Kh. Kelini Revision and editing: Hosnia S. Abdel-Mohsein, Manal A. M. ahmoud and Zakaria M. Zaky. Paper submission: Wafaa Kh. Kelini

Conflict of interest

The authors declare that there was no conflict of interest for publication of an article. We stated that the manuscript has been read and approved by all authors; also we have no financial fund of support.

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