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Egypt. J. Bot., **Vol. 59,** No.3, pp. 551-566 (2019)

Egyptian Journal of Botany
http://ejbo.journals.ekb.eg/

Toxicological Studies on Microcystin Produced by *Microcystis aeruginosa*: Assessment and Management

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MICROCYSTIS aeruginosa is a kind of cyanobacteria microorganism that synthesizes and produces peptides, which could be highly toxic. The most common toxin known as microcystin (MCs) or cyanotoxins, these toxins are heptapeptides produced by cyanobacterial blooms on water surfaces. They potentially lead to acute to chronic health-related problems via increasing reactive oxygen species (ROS) and irreversible inhibition of serine/threonine protein phosphatases. The toxicological studies of MCs on experimental animal and cell models have promise interests; however, few information is known about their impacts on humans due to acute or chronic exposure. This review article aimed to present some of the information about the cyanotoxins structure, occurrence, and distribution of the cyanobacterial toxins especially excreted from *M. aeruginosa*. Also, toxicological studies and investigations associated with *M. aeruginosa* producing microcystin, their assessments and control and health problems and cancer risk upon MCs exposure will be discussed. The article will also discuss the mechanism of the toxin and the way for control and degradation.

Keywords: Toxicity, Cyanobacteria, Microcystin, *Microcystis aeruginosa.*

Introduction

Cyanobacteria are blue-green algae naturally occurring in shallow, nutrient-rich water, some of them produce toxins that could harm animals and humans (Stotts et al., 1993). Some of these cyanobacteria such as *Microcystis, Planktothrix, Cylindrospermopsis* and *Anabaena* generate an array of toxic products. However, some genera can develop scums, blooms, and mats in water bodies for human use, they are a rich source of biomedically active constituents that showed antitumor, antibiotic, and antiviral activities (Moore et al., 1996; Metcalf & Codd, 2012). These blue-green algae produce secondary metabolites like polyketides, non-ribosomal peptides, ribosomal peptides, isoprenoids and alkaloids (Kultschar & Llewellyn, 2018; El-Sheekh et al., 2012a). As cyanobacteria grow and die, the cell walls burst and their cyanotoxins produced and can be released into the water. Toxin concentrations can become elevated, particularly during a bloom event, concentrate along shorelines, and can persist in the environment. The exposure pathway for cyanotoxins is mainly through the ingestion of polluted water, where scums tend to accumulate. Skin contact with cyanobacteria results in a dermal irritant or allergic effects; however, the cyanotoxins are not likely to cross the skin barrier and enter the bloodstream. Inhalation and aspiration of the toxin are also possible.

Microcystin (MCs) is a cyclic heptapeptide hepatotoxin, which reported from different places all over the world (Lopez-Archilla et al., 2004; Tyagi et al., 2006; Herry et al., 2008; Lalita et al., 2009; Kumar & Verma, 2012; Chaturvedi et al., 2015; Harke et al., 2016). These MCs produced

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Received 21/10/2019; Accepted 12/11/2019
DOI: 10.21608/ejbo.2019.18478.1371
Edited by: Prof. Dr. Salama A. Ouf, Faculty of Science, Cairo University, Giza 12613, Egypt.

by specific species of cyanobacteria belonging to the following genera *Anabaena, Microcystis, Nostoc*, *Planktothrix* and *Nodularia* (Rouhiainen et al., 2004; Tyagi et al., 2006; Chaturvedi et al., 2015). The most common species of cyanobacteria produce MCs toxins called *Microcystis aeruginosa* and the most common MCs known as microcystin–LR (MC-LR), *M. viridis* and *M. botrys* strains also have been shown to produce MCs (Trogen et al., 1996; WHO, 1999; Deyab et al., 2019). At the molecular level, MCs could potentially inhibit protein phosphatases activities. MCs localized in two *M. aeruginosa* strains by Shi et al. (1995); toxin-producing strain (PCC 7820) and non-toxin producing strain (UTEX 2063) by using a polyclonal antibody in conjunction with immuno-gold labeling. The production of these toxins is influenced by some physical and chemical factors as well as nutrients supplements that reported by laboratory studies (Sivonnen, 1990; Utkilen & Gjolme, 1992; Paerl & Otten, 2013). The change in temperature associated with the stress levels that promote variations in the toxin's concentration and composition (Yokoyama & Park, 2003). Van der Westhuizen & Eloff (1985) reported that the highest growth rate of *M. aeruginosa* achieved at 32˚C, the highest toxicity found at 20˚C. The light intensity influences the cellular structures of *M. aeruginosa*, different light intensities alters pigments ratio, which in turn causes photo-oxidation of these photosynthetic pigments (Abelovich & Shilo, 1972). Kaebernick et al. (2000) reported that 16µmol photons/ms in the red-light spectrum, increase toxin production in a *M. aeruginosa* strain. The most pronounced effect of chemical factors on the *M. aeruginosa* toxicity is the nutrients ratio alterations. Carmichael (1986) reported that the deprivation of nitrogen sources causes a decrease in toxins production. Furthermore, cyanobacteria compensate iron stress, by new polypeptides synthesis (Lukač & Aegerter, 1993). There is not enough information to determine the risk of consuming toxigenic cyanobacteria. This chapter will discuss toxicology, assessment, and management of the cyanobacterium *M. aeruginosa*.

Microcystins (MCs) structure

The MCs are non-ribosomal peptides, synthesized by a complex multifunctional enzyme encoded on microcystin synthetase (*mcy*) gene cluster of variable composition and organization (Christiansen et al., 2003; Rouhiainen et al., 2004; Pearson et al., 2010). Due to these genes' variability, over 70 structural variants of MCs are characterized (Welker & von Dohren, 2006). The heptapeptide MCs are composed of D–alanine, two variable L–amino acids, γ–linked D–glutamic acid and 3 unusual amino acids. Over 50 different MCs were characterized that vary in the two L-amino acids at positions 2 and 4, and methylation/demethylation (Fig. 1).

The unusual amino acid Adda ((2S,3S,8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid) is essential for the expression of biological activity (Trogen et al., 1996; McElhiney & Lawton, 2005; Welker & von Dohren, 2006). There are more than 240 MC variants of the new analogs are still being discovered (Spoof & Catherine, 2017). The linear MCs are more than 100 times less toxic than the equivalent cyclic compounds; these linear MCs are thought to be MCs precursors and/or bacterial breakdown products (Choi et al., 1993; Rinehart et al., 1994; Bourne et al., 1996).

Occurrence and distribution of MCs

Globally, MCs can be found in freshwaters as well as marine habitats. Cyanotoxins have also been reported in desert environments (Metcalf et al., 2012). The occurrence of MCs has been reported from different areas all over the world (Kaasalainen et al., 2012). Particularly, the occurrence of toxic blooms was discovered in the nineteenth century in South Australia (Francis, 1878). The most commonly found cyanobacterial toxins in blooms are the cyclic peptide toxins of the MCs family that cause a major challenge to produce safe drinking water.

The presence of different MCs was investigated in Lake Mokoan, Australia (Jones et al., 1995) and Homer Lake bloom, U.S.A. (Namikoshi et al., 1995). The occurrence of MC-LR from four drinking water reservoirs in southern California (USA) has been discovered by Izaguirre et al. (2007). Toxin-producing cyanobacteria have discovered in 12 water bodies in Kenya with considerable levels of MCs (Kotut et al., 2006; 2010). Different variants of MCs have also been reported from calcareous streams and rivers (Aboal et al., 2005; Marco et al., 2012). Mohamed & Al Shehri (2007) have also demonstrated the presence of MCs in the cyanobacterium from open treated-water storage reservoirs in Abha city, Saudi Arabia by using ELISA and HPLC analysis. Vasconcelos et al. (2010) have reported the MCs

profiles in various aquatic ecosystems in Central Mexico. Hodoki et al. (2012) have determined the production of MCs by some strains of Microcystis from Japanese lakes. Furthermore, cyanobacterial blooms and production of MCs has been reported from several African countries such as Tunisia, Algeria, Morocco, Ghana, Nigeria, Uganda (El Herry et al., 2008; Nasri et al., 2008; Oudra et al., 2009; Addico et al., 2009; Indabawa, 2010; Okello et al., 2010), European countries (Pavlova et al., 2006), Serbia (Svirc˘ev et al., 2009) and several Asian countries such as Iraq and Singapore (Al-Sultan, 2011; Mohebbi et al., 2012).

Microcystins assessment

Microcystins (MCs) can be mainly extracted by using different solvent mixtures including a mixture of acidified aqueous methanol solution (methanol/water/trifluoracetic acid), or 75% acetonitrile (ACN). The optimum composition of the extraction solvent mixture was found to be 80/19.9/0.1 (v/v/v) for MC-LR, MC-RR and MC-YR (Li et al., 2014). Furthermore, it has been reported the extraction of MCs from different tissues (gills, liver, intestine, muscle) using a mixture of water:methanol:butanol (75:20:5) (Cadel-Six et al., 2014).

Several methods used for microcystin determination, for instance, mass spectroscopy (MS), high-performance liquid chromatography (HPLC), sequencing by direct DNA test, enzyme-linked immune-sorbent assay (ELISA) (Nishizawa et al., 2000). ELIZA is one of the most important techniques using the fluorescent probe to determine protein phosphatase inhibition (Dawson, 1998). This available assay uses the direct monoclonal (DM) ELISA which cross-reactive with all MC variants. By detection of MCs by anti-Adda ELISA, a false positive can occur, due to cross-reactivity with Nodularins; they can give rise to an overestimation of the toxic potential also due to cross-reactivity with the GSH-conjugates (Preece et al., 2015).

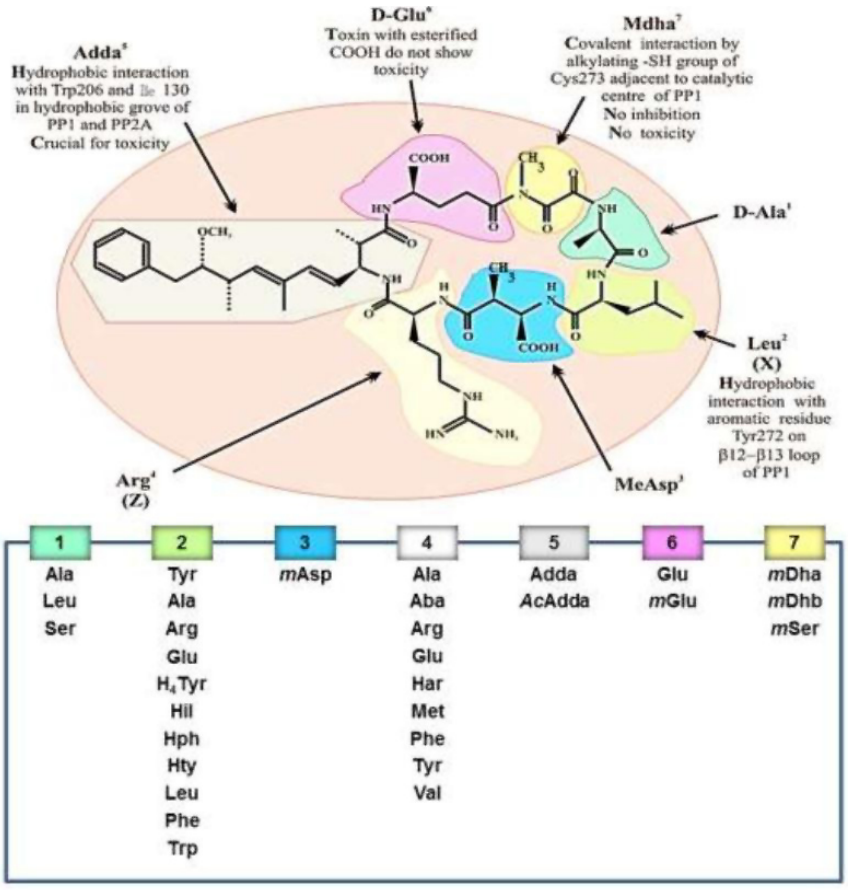

Fig. 1. Schematic structure of microcystin (MC-LR), adapted by McElhiney & Lawton (2005), Welker & von Dohren (2006).

The protein phosphatase inhibition assay (PP1c) is based on the ability of MCs to inhibit Serine/Threonine protein phosphatase. Williams et al. (1997) used PP1c assay on mussel extracts in a ^{32}P-radiolabelled phosphorylase a phosphatase (PPase) bioassay to determine the quantity of MCs. The inhibition of Ser/Thr protein phosphatase by MCs in particulate and fish extracts was assessed also by a fluorometric method as described by Berry et al. (2011). The colorimetric immune protein phosphatase inhibition assay (CIPPIA) method could specifically target the inhibitory activity MCs towards protein phosphatases. The ability of MC-LR antiserum to protect PP1 from the inhibitory action of microcystin-LR and related cyanobacterial toxins was used as the basis for the CIPPIA procedure (Metcalf et al., 2001).

Polymerase chain reaction (PCR) used for MC-RL detection and for discrimination between the toxic microcystin-producing and non-toxic strains by using the mcy gene primers (Baker et al., 2002; Pan et al., 2002). In addition, an accessible colorimetric method was described to screen human serum for microcystin exposure evidence (Hilborn et al., 2005). Sangolkar et al. (2006) were applied other instrumental and molecular methods for determining the peptide hepatotoxins (microcystins) and microcystin-producing cyanobacteria. It has been developed a procedure to detect the total MCs in human samples using a combination of ELISA, liquid chromatography and liquid chromatography-mass spectrometry (LC/MS), gas chromatography (GC/MS) and MS/MS techniques (Yuan et al., 2006). The use of LC-MS for the detection of MC content in sample extracts has been reported (Wu et al., 2010; Cadel-Six et al., 2014). Tippkötter et al. (2009) developed a fast detection assay method of MC-LR by immunochromatographic lateral flow dipstick assay to an anti-MC-LR antibody. Gold particles with diameters range of 40nm were used as red-colored antibody labels for the visual detection of the antigen. Recently, Facciponte et al. (2018) characterized aerosolized cyanobacteria in the respiratory system of humans.

Mechanism of toxicity mediated by M. aeruginosa

Blooms of *M. aeruginosa* and their associated toxins have long been recognized as a problem for aquatic systems, previous studies have demonstrated significant and severe impairment in coastal receiving waters (Miller et al., 2010; Gibble & Kudela, 2014). Toxins generated by *M. aeruginosa* have different mechanisms of toxicity, they can target different cells and organs, classified due to their mechanism of action into hepatotoxins, neurotoxins, dermatoxins, and cytotoxins (Carmichael, 1992; Codd et al., 2005; Metcalf & Codd, 2012). The targeted tissues especially liver could uptake MCs through transporters for instance, the organic anion transporting polypeptide superfamily (OATPs) into the hepatocytes via (OATP1B1, OATP1B2, and OATP1B3) and across the blood-brain barrier (OATP1A) (Fischer et al., 2005; Komatsu et al., 2007; Lu et al., 2008). Then de-regulates serine/threonine protein phosphorylation via serine protein phosphatases 1 and 2A inhibition irreversibly by covalent binding (MacKintosh et al., 1990, 1995; Bagu et al., 1997) (Fig. 2).

The imbalance causes increase in the amount of phosphorylated protein and cellular damages due to the strong interaction between the toxins and phosphatases enzymes, which in turn leads to massive hemorrhage and therefore affect energy production, cellular metabolism, gene expression and translation (Honkanen et al., 1990; Yoshizawa et al., 1990; Romanowska-Duda et al., 2002). The phosphatase inhibiting effects of microcystins also harm plant phosphatases (Siegl et al., 1990). Runnegar et al. (1993) reported the relation between microcystins administration and phosphatases activity inhibition. They treated mice with MC–LR to and determined the inhibition of liver protein phosphatase 1 and 2A activities. Also, confirmed by clinical changes due to intoxication with microcystin. Protein phosphatases inhibition leads to the redistribution of proteins. It has been reported that treatment with microcystin led to cytoskeletal actin microfilaments in rat's hepatic cells (Ghosh et al., 1995).

Hermansky et al. (1991), studied the mechanism of toxicity action mediated by MCs when observed a decrease in the membrane fluidity of liver microsomes, upon treating mice with MC–LR. Furthermore, a rapid decline in cardiac output was reported in MC–LR intoxicated rats accompanied by acute hypotension and acute drop in heart rate (LeClaire et al., 1995). It has been reported that MCs exposure led to oxidative stress in the cells and imbalanced the oxidant/antioxidant ratios due to the generation of reactive oxygen species (ROS) (Campos & Vasconcelos, 2010a). Therefore, oxidative stress seems to be another important biochemical mechanism of

MCs toxicity that mediated by ROS, which might cause serious cellular damage such as peroxidation of lipid membranes, genotoxicity, or modulation of apoptosis (Ding & Ong, 2003). The generation of ROS is the most likely mechanism responsible for genotoxicity, oxidative DNA damage, and clastogenic effects of MCs (Humpage et al., 2000; Bouaicha et al., 2005) (Fig. 2).

During the chronic exposure to MCs, the diacylglycerol (DAG) pathway activated the protein kinase c (PKC), which enhances cell proliferation and induce tumors (Deng et al. 1998). The MCs regulates mitogen-activated protein kinases (MAPK), by inhibiting phosphatases activity, which in turn alter proteins phosphorylation in the cell cycle (Gehringer, 2004; Kumar et al., 2005). In addition, MCs alters in the expression of the tumor suppressor gene (*p53*) that could share in MC-LR induced tumor genesis (Hu et al., 2008).

While in the case of acute exposure to MCs, oxidative stress and apoptosis triggered by the mitochondrial pathway, ROS production, activation of Ca^{2+}/calmodulin-dependent kinase 2, and lysosome involvement (Ding et al., 2000; Billam, 2006; Morselli et al., 2008; Alvarca et al., 2009; Svirc˘ev et al., 2010).

Health problems and cancer risk upon MCs exposure

The emergence of MCs toxin as both stable in marine receiving waters and harmful for upper marine trophic levels, including apex predators and humans, highlights the need for a better understanding of their effects on humans and wildlife health. The MCs can even persist and still active after boiling, therefore cooking is not enough to destroy the toxins (WHO, 1999). The MCs have been studied for their possible toxic effects due to existence in water. Several studies reported the negative impacts and health problems of cyanobacterial toxins (Vasconceles et al., 2001; Alonso-Andicoberry et al., 2002; Krienitz et al., 2003). It causes acute poisoning, tumor promotion and growth, cytolysis/apoptosis, cytoskeleton loss, genotoxicity and cellular damage. Upon the entrance of MCs into the human body orally, they absorbed through the small intestine and then reabsorbed into the portal bloodstream to the liver (Falconer & Yeung, 1992). This led to functional damage to the hepatocytes and resulted in autophagy, apoptosis, necrosis, or cell proliferation, depending on the dose and duration of exposure, the sub-lethal doses induce apoptosis via ROS generation and the high doses causes' hepatocyte necrosis (Svirc˘ev et al. 2010).

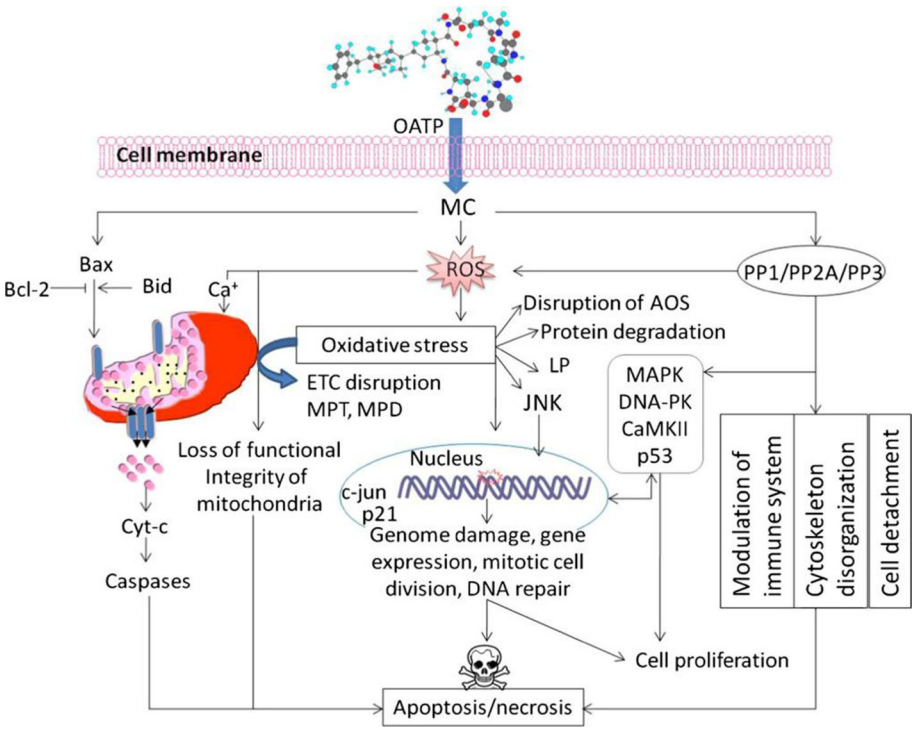

Fig. 2. Schematic representation of MCs mechanism of actions adapted by Rastogi et al. (2014).

Toxicity of MC was also focused on organ toxicity other than the liver (e.g. reproductive and thyroid toxicities), in some cases with administration of a single dose by using the intraperitoneal (i.p) route of exposure has marked kinetic differences (up to 30 fold) with respect to acute toxicity when compared to the oral route. Based on the WHO, Tolerable Daily Intake for chronic exposure of 0.04µg/kg bw/day. Up to 5.6µg MCs/kg fish was limited for an adult body weight of 60kg, daily consumption of fish of 86 g and intake of water. and 1.4µg/kg of fish for children (default bodyweight of 10kg and daily consumption of 57g) (Gaudin et al., 2008; AFSSA, 2009; Chorus, 2012).

Several health problems such as pneumonia dermatitis and hepato-enteritis allergic reaction and gastroenteritis might result from consuming water contaminated with cyanobacteria-produced toxins (Bell & Codd, 1994; Tyagi et al., 2006). Some of MCs are neurotoxins, which could inhibit cholinesterase enzymes and block sodium channels, which inhibit nerve conduction (Carmichael, 1994). Symptoms that appeared upon intoxication with MCs are vomiting, diarrhea, weakness, and piloerection (Bell & Codd, 1994). *In vivo* and in *vitro* toxicity studies showed disruption in the normal hepatocytes architectures with a high apoptotic rate in rat hepatocytes after treatment with MC-LR (Romanowska-Duda et al., 2002). In a previous study Ueno et al. (1996) revealed that MC-LR (0.01µg/L) in drinking water correlation with primary liver cancer, however, World health organization (WHO) appointed that the concentration of MC-LR in drinking water should not increase 1µg/L (WHO, 1998).

Several studies on experimental animals (rodents, pigs) showed significant toxicity of orally administered MCs, where harmful impacts of MCs such as increased mortality, liver injury (degeneration of hepatocytes, increased liver enzyme levels, histopathological changes, chronic inflammation), renal damage or slightly higher number of tumors were observed (Fawell et al., 1999; Falconer, 2006). Toxicity of MCs and carcinogenesis potentiality have great interest from researchers (Falconer, 2007; Gaudin et al., 2008; Li et al., 2009; Campos & Vasconselos, 2010b; Takumi et al., 2010; Zhang et al., 2012). Interestingly, MCs reported as pro-carcinogenic agents that stimulate the proliferation of cancer cells and cause DNA damage (Zegura et al., 2003, 2012 and 2016). Therefore, MCs are tumor promotion factors; there has been evidence of tumor promotion properties of MCs from several animal experiments (Humpage et al., 2000; Dietrich & Hoeger, 2005). Mice topically treated with dimethylbenzanthracene and treated with *Microcystis* extracts have an increase in skin tumors (Falconer, 1991). Furthermore, extracts from *Microcystis* caused a dose-dependent increase in the percentage of liver tumors (Nishiwaki-Matsushima et al., 1992). However, extracts of *Microcystis* decreased duodenal tumors in mice (Falconer & Humpage, 1996). These findings are supported by results of studies showing effects of MCs on cell proliferation and cytokinesis, which might be associated with tumor promotion (Gehringer, 2004; Guzman et al., 2003). Moreover, in epidemiological studies, the incidence of colorectal or liver cancer was related to the consumption of water originated from sources contaminated with microcystin or MC-producing cyanobacterial blooms (Zhou et al., 2012).

Impacts of M. aeruginosa on other living organisms

M. aeruginosa produces toxic, bioactive secondary metabolites that can harm the life of most organisms of the ecosystem and aquatic health (Holland & Kinnear, 2013; Gibble et al., 2016). The toxicity of MCs affects a wide range of organisms including invertebrates, fishes and birds. The MCs accumulation in invertebrates as *Procambarus clarkia* or *Mytilus galloprovincialis* seems to be quite fast. *Mytilus galloprovincialis* showed resistant to MCs (Amorim & Vasconcelos, 1999; Vasconcelos et al., 2001). These cyanotoxins cause several physiological, biochemical and behavioral changes in freshwater invertebrates. MCs accumulation in tissues can be transferred through the food chain to animals led to toxicity.

Bownik (2013) reported the negative influences of MCs on crustaceans, zooplankton and mollusks indicating the ecotoxicological consequences on the aquatic environment. It has been proved that oral administration of MCs to fish led to hepatic necrosis and death (Tencalla et al., 1994). Hu et al. (2017) evaluated the effects of *M. aeruginosa* toxicity on *Hypophthalmichtys molitrix* (silver carp) by using hepatic RNA-seq and miRNA-seq. Furthermore, it has been reported that *M. aeruginosa* alters some biochemical markers of *Oreochromis niloticus*

(Marzouk et al., 2013). Shrimps exposed to toxic *M. aeruginosa* showed histological lesions development in gills, glands, lymphoid organs and muscle that may interfere with respiration, food absorption, excretion, locomotion and cause death (Morales-Covarrubias et al., 2016). Zhao et al. (2014) determined the adverse effects of *M. aeruginosa* on rotifers due to the presence of MCs. Oberemm et al. (1997) reported that MCs could alter fish eggs development. *M. aeruginusa* caused chickens death upon oral administration (Gorham, 1960). El-sheekh et al. (2013) determined the adverse effects of *M. aeruginosa* toxins microcystin-LR on the germination, growth and chlorophyll content of *Zea mays*. They found a significant reduction in the root, shoot lengths, number of lateral roots, dry and fresh weight and pigment content. Also, Microcystins from *M. aeruginosa* affected the growth and production of polysaccharides by tested algae *Anabaena* sp*., Oscillatoria angustissima, Scendesmus obliquus* and *Chlorella vulgaris* (El-Sheekh et al., 2012b). El-Sheekh et al. (2014) also demonstrated that Microcystin toxin from *Microcystis aeruginosa* induced inhibition of mitotic index in *Allium cepa* root tips in addition, chromosomal abnormalities were observed.

Control of M. aeruginosa and ways of degradation

Laboratory studies showed that the degradation of MC-LR toxins produced by *M. aeruginosa* occurred in one week (10mg/L). Their stability observed in deionized water for over 27 days and in sterilized reservoir water over 12 days. Therefore, the reservoir water instability was due to biodegradation (Cousins et al., 1996). Lam et al. (1995) found that MC-LR present in cells remains inside the cell until the cell lysis occurred. Significant degradation of these toxins achieved by sunlight irradiation due to isomerization of a double bond in the Adda-side chain in cyanobacteria within half-life for about ten days. Furthermore, the rapid degradation of MC-LR was found upon UV light (238-254nm) exposure (Tsuji et al., 1995).

Chemical control of *Microcystis* blooms gives the best solution for MCs degradation. Some chemicals used to control cyanobacteria blooms, such as $CuSO_4$, NaOCl, $KMnO_4$ that inhibit the enzymatic reactions and the synthesis of the cell wall (Kenefick et al., 1993; Lam et al., 1995). It has been proved that copper is effective in the chemical control of *M. aeruginosa toxicity* by examining their cellular ultra-structures (Verhoeven & Eloff, 1979). Copper also decreases the nucleoplasm density, as well as cause DNA aggregation. Ozonation combined with filtration was efficient in removing toxic cyanobacteria from water by providing oxidation potential enough to destroy the toxin present in *M. aeruginosa* ($5x10^{-5}$ cells/ml) (Hoeger et al., 2002). Very high chlorine concentrations could inactivate the microcystins. In addition to chemical control, biological control is a promising approach in *M. aeruginosa* bioremediation. Natural populations of microorganisms and biofilms could degrade Mcs within two weeks (Lam et al., 1995; Saitou et al., 2002). Gandhi & Kumar (2016) revealed for the first time the potentiality of bacteria in Mcs bioremediation, which called Mcs-degrading bacteria in water bodies.

The chrysophyte *Ochromonas danica* reported declining *M. aeruginosa* growth by ingestion (Cole & Wynne, 1974). A report documented the potential of using barley straw for cyanobacterial control especially *M. aeruginosa* by significant inhibition of their growth rate due to certain phenolic contents (Newman & Barret, 1993). Harding & Plaxton (2001) reported also a significant reduction in algae populations within a few weeks upon the application of hay in the water bodies.

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دراسات السمية على الميكروسيستين المنتج من طحلب الميكروسيستس اوريجينوزا: التقييم والإدارة

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ميكروسيستس اوريجينوزا هو نوع من أنواع السيانوبكتريا الذي يصنع وينتج البيبتديتات والتي تعتبر سامة جدا. ويعتبر السم الطحلبى المعروف باسم الميكروسيستين الذى ينتج بواسطة النمو الزائد للسيانوبكتريا على سطح المياه. وهذه السموم من المحتمل أن تؤدي إلى مشاكل حادة مرتبطة بالصحة من خلال زيادة أنواع من الأكسجين التفاعلى وتثبيط فسفاتاز بروتين سيرين / ثريونين. وتعتبر دراسات السمية على الميكروسيستينات في حيوانات التجارب ونماذج الخلايا ذات اهتمام مبشر ولكن معلومات قليلة معروفة عن آثارها على البشر بسبب التعرض الحاد أو المزمن. تهدف هذه المقالة المرجعية إلى تقديم بعض المعلومات حول تركيب السموم السيانويكتيرية، تركيب، تواجد وتوزيع هذه السموم التي تفرز بشكل خاص من الميكروسيستس ا اوريجينوزا. أيضا ستتم مناقشة الدراسات والتحقيقات السمية المرتبطة بـالميكروسيستس ا اوريجينوزا المنتج للسموم وتقييماتها ومكافحتها والمشاكل الصحية ومخاطر السرطان عند التعرض لهذه السموم. سوف يناقش المقال أيضًا آلية السمية وطريقة التحكم والتكسير الحيوى.