INTRODUCTION

Cyanobacterial harmful algae blooms have been recognized as a problem worldwide, resulting from the inherent detrimental effects, although the presence in the ecosystem is not widely recognized. Cyanobacteria, also known as blue-green algae (N. A. Herrera et al., 2015) are a group of bacteria characterized by numerous structural features (El Gamal, 2010). These microorganisms are autotrophic, which are primary producers in aquatic systems, hence categorized as algae (Picardo et al., 2019). Also, due to the chlorophyll a content and the presence of related compounds (El Gamal, 2010), cyanobacteria are able to perform photosynthesis, which is a process that provides the primary source of energy for most forms of life on Earth (Axmann et al., 2014). Meanwhile, other forms yield a variety of toxic and possibly harmful compounds, in the form of secondary metabolites, termed cyanotoxins, attributed as one of the most important groups of natural toxins (Picardo et al., 2019; Kimambo et al., 2019; EPA, 2015a; Griffith & Gobler, 2020). Therefore it is necessary to establish microcystin exposure pathways, which summarize several studies on the dangers, to enhance the ease of understanding.

Some strains have very rich chemistry and are capable of producing a wide range of bioactive compounds with varying properties (El Gamal, 2010; Picardo et al., 2019), of which some are beneficial and have been applied in many valuable products (Axmann et al., 2014). Meanwhile, other forms yield a variety of toxic and possibly harmful compounds, in the form of secondary metabolites, termed cyanotoxins, attributed as one of the most important groups of natural toxins (Picardo et al., 2019; Kimambo et al., 2019; EPA, 2015a; Griffith & Gobler, 2020). Therefore it is necessary to establish microcystin exposure pathways, which summarize several studies on the dangers, to enhance the ease of understanding.

Morphologically, blue-green algae have been identified in diverse forms, including filamentous (Kumayer et al., 2016), unicellular (Atteia et al., 2013), colony as well as multicellular, and they are taxonomically grouped under prokaryotes (Bortoli et al., 2014). These microorganisms are considered as gram-negative, despite the demonstration of both gram-negative and gram-positive properties using electron microscopy.

ALGAL BLOOM

Environmental Factors

The continuous aging of water bodies has been attributed to natural and anthropogenic activities (Martins et al., 2017;
Sinha et al., 2018). This also affiliated with alteration in
land-use practices, urbanization, and agricultural activities,
which tend to change the sediment loading, as well as increase
nutrient delivery in watersheds. Finally, great changes are
experienced due to eutrophication (Herrera et al., 2015;
Janssen et al., 2014), and climate change (Aguilera et al., 2018).
This eutrophication is considered to pose serious threats 16,
and known to influence the growth of cyanobacterial (Clark
et al., 2017), which consequently forms the algal bloom
(Merel et al., 2013; Song et al., 2009; Wilkinson et al., 2020)
that defined as the rapid and uncontrolled growth of algae
(Bennett, 2017).

This algal bloom is strongly influenced by environmental
conditions, including temperature (Dreher et al., 2019; EPA,
2015a; EPA, 2015b; Scavia et al., 2014; Song et al., 2009),
light intensity, pH, salinity, dissolved oxygen (Griffith
& Gobler, 2020; Scavia et al., 2014), changes in species
diversity (Ritson et al., 2014), turbulence nutrients, e.g.,
nitrogen (Gobler et al., 2007), phosphate (D’Angelo &
Wiedenmann, 2014) and carbon (Merel et al., 2013), as
well as competing/grazing of bacteria and phytoplankton
(Gobler et al., 2007; Ramanan et al., 2016). The affected
ecosystems are often characterized by the presence of
cyanotoxins (Janssen, 2019).

Presence and Movement

Currently, many people assume the growth of cyanobacteria
is constrained to aquatic ecosystems. Cyanobacterial blooms
have increased in frequency worldwide within the last decades,
posing a threat to water supplies and recreational areas (Aguilera
et al., 2018; Janssen et al., 2019; Picardo et al., 2019). These
microorganisms are produced in most aquatic ecosystems,
including lakes (Scavia et al., 2014; Zhang et al., 2012),
reservoirs (Takahashi et al., 2014), ponds (Clark et al., 2017),
lagoon (Paldavičienė et al., 2015), rivers (Picardo et al., 2019),
estuarine (Preece et al., 2017), bay (Estepp & Reavie, 2015),
and oceans (Bennett, 2017). However, research has proved
cyanobacteria adaptability to a wide range of habitats, there
in water, soil, air, corals (Radecker et al., 2015), and also in
the chips for laboratory-scale research with the addition of
nutrients resembling the natural conditions (Girault et al.,
2019). There is growth potential in areas with very low water
content, arid environments, alongside tolerability to high
salinity, as seen in hypersaline ponds (Subashchandrabose et
al., 2013).

Several factors have a significant impact on the presence of
cyanobacteria in air, providing information on the emission
effectiveness, transport, and deposition (Wiśniowska et al.,
2019). These microorganisms also have the capacity to moving
along the water column (Wilkinson et al., 2020), and precipitate
out, after residing in the sediments for months, and even years,
at a concentration of approximately one order of magnitude
higher than the value recorded for surface water (Takahashi
et al., 2014).

MICROCYSTIN

Classes

There are four classes of cyanotoxins with a high impact on
drinking water, encompassing microcystin, cylindrospermopsin,
anatoxin, and saxitoxin (He et al., 2016). In addition,
cyanobacteria produces an incredible diversity of peptides and
other compounds (Miles et al., 2013), although only microcystin
has been intensively studied. This consists of over 80 variants
(Kist et al., 2012) with 100 different congeners 10, of which
microcystin–LR (MC-LR) stands out for the high distribution
and toxicity (Martins et al., 2017), followed by MC-YR, MC-LA,
MC-YM and MC-RR 1. Furthermore, MC-LR has a provisional
limit of 1 mg/L, based on the recommendation of World Health
Organization (WHO) (Tsagkaris et al., 2019), although all are
considered as toxins (Kist et al., 2012; Weng et al., 2019) due
to the possibility of poisoning in humans and animals as well
as plants (Fontanillo & Köhn, 2018).

Photolysis and Hydrolysis

Cyanobacteria are phototrophic microorganisms (Merel et al.,
2013). The microcystin reported undergoes a slow photochemical
breakdown in the presence of full sunlight. This the reason for
the low vulnerability of groundwater to form algae compared
with surface waters, for the deeper sources are characterized by
a slower rate of a possible breakdown. The process velocity is
depending on the pigment concentrations, light intensity, humic
substances, and microcystin congener. Moreover, cyanobacteria
exhibit a strong resistance for the extreme habitats, as a study
shows the survivability of cyanobacteria in the outer space, and
also under UV radiation within 548 days (Ramanan et al.,
2016).

Some cells are capable of migrating to the marine environment,
lyse, and further release toxin into the water (Gibble & Kudela,
2014). Most toxins are intracellular, which is discharged following
the rupture or death of the cell, while the extracellular forms
comprise less than 30% of the total microcystin concentration
in the source water. Conversely, both varieties are possibly
present in treated water, depending on the handling processes.
Microcystin is reported as relatively stable and resistant to
chemical hydrolysis or oxidation at near-neutral pH, while
higher or low pH values and temperatures above 30°C have
been affiliated with slow hydrolysis.

Metabolism

Microcystin conjugates with glutathione and cysteine to increase
solubility and facilitate excretion. Moreover, several studies
have investigated the role of glutathione homeostasis and lipid
peroxidation in microcystin-induced liver toxicity. However,
as the potential risk of numerous cyanobacterial metabolites
remains unknown. These processes are versatile, featuring rapid
switching between modes (Subashchandrabose et al., 2013).
Some scientists have affiliated the removal of microcystin to
the incidence of biodegradation, as some bacteria have been
reported capable of decomposing MC-LR. These include
Arthrobacter, Brevibacterium, Rhodococcus, Paucibacter, Sphingomonas (Pseudomonas).

**Sources and Pathways**

Microcystin-RR identified in most soils (Xiang *et al.*, 2019), which is introduced through contacts with land plants by agriculture activities, especially along with contaminated irrigation water sources (Cao *et al.*, 2018). This has led to high land invasion (Gibble & Kudela, 2014), characterized by the occurrence of microalgae on buildings, trees or roofs (Wiśniewska *et al.*, 2019).

Furthermore, microcystin also can spread into the surrounding environment (Takahashi *et al.*, 2014), especially for the aerosolized cyanobacteria, which is passively transported through the air. The vitality of these organisms depends on adaptation and the ability to react actively to the changing environmental conditions (resilience) (Fröhlich-Nowoisky *et al.*, 2016). Also, cyanobacteria are mainly emitted into the atmosphere from water surfaces, and soil (Wiśniewska *et al.*, 2019).

Exposure to cyanotoxins occurs through absorption, dermal, respiratory/inhalation, and hemodialysis/intravenous, while some research concluded oral/ingestion of contaminated drinkable water and food as the main source. These possibly lead to acute or chronic toxicity in humans and animals (Picardo *et al.*, 2019), while the use of Microcystin-contaminated irrigation water was identified as the dominant pathway of accumulation in vegetables and soils.

Facilitated transport is necessary for uptake of Microcystin into organs and tissues, as well as for export. Several studies have produced information on the possible distribution through the digestive, respiratory and circulatory tracts. Microcystin was also detected in the villi of the small intestine, blood plasma, liver, lungs, kidneys, gill tissue, ileum, heart, large intestine, and spleen. The toxin is capable of inducing damage to distribution tissues, including vascular structures and gills (Martins *et al.*, 2017). While in plants, based on the study conducted on rice plants, the greatest concentrations of microcystin was recognized in the leaves, following a process translocation from the roots (Cao *et al.*, 2018).

**Bioaccumulation**

This process is possibly affected by various factors, including the exposure route, duration, and concentration of Microcystin in their food resources (Dong *et al.*, 2012), as well as bioaccumulation capacity and incomplete depuration after contact (Paldavičiene *et al.*, 2015). The toxin accumulates on the seafloor (Takahashi *et al.*, 2014), in snail (J. Zhang *et al.*, 2012), in fish tissues (Dong *et al.*, 2012), in various mammal organs, including muscle, liver, kidney, heart, lung, spleen, gastrointestinal tract and gonads, consequently leading to potential damage. Microcystin also affects vegetables and soils (Xiang *et al.*, 2019), rice (Cao *et al.*, 2018), cereals, corn, peanuts, soybeans, and spices, among others during maturation, storage, and transportation (Picardo *et al.*, 2019). This toxin biomagnifies and persists in the medium of co-occurrence, and poses a large potential ecological risk within the food chains (Gibble & Kudela, 2014; Z. Wang *et al.*, 2017). Furthermore, cyanotoxin persistence after agricultural land applications require urgent attention (Quilliam *et al.*, 2015).

Microcystin is potentially risky to life and the environment, and the following considerations were reported in some studies:

1) Death (Vasconcelos *et al.*, 2013), which occurred to the steers (Dreher *et al.*, 2019) and the freshwater terrapin species (Nasri *et al.*, 2008).

2) Genotoxicity effect, where continuous exposure to low concentrations of purified microcystin extracts, activates cellular oxidative stress, subsequently causing genotoxicity and other mutagenic action.

3) Damage to organs and tissues has been observed in the immune and brain cells of mammals (Takser *et al.*, 2016), cardiac, lung, intestine and spleen of mice (Al-hazmi, 2020), male reproductive system (testis) (Lone *et al.*, 2015), and also the antioxidant enzymes in fish; in the order of liver > gill > muscle (Isibor, 2017).

4) Growth reduction was reported in plants exposed to microcystin, which significantly decreased root growth and activity, featuring induced lipid peroxidation, and also a decline in the crown and lateral root number (Cao *et al.*, 2018). While in yellow catfish experienced a significant reduction in growth rate after 30 days of dietary exposure (Dong *et al.*, 2012).

A study established the poor tendency from low-dose exposure to Microcystin-LR administered over long-term to cause chronic liver disease in normal liver, or exacerbate existing hepatitis (Labine *et al.*, 2017). Conversely, there were different opinions on the sufficiency for low concentrations present in the environment to promote severe damage in organisms (Pamplona-Silva *et al.*, 2018). This study, therefore, affiliates the health risks with the dosage, which is also posed by repeated exposure.

Despite the numerous studies on cyanobacteria, not much is explained about the direct effects on humans, as most investigations were conducted with animals and plants. This limitation is due to a lack of information on other exposure, and also uncertainty regarding the adequate control for confounding factors during the study. These include Hepatitis B infection, as well as industrial and wastewater discharges to the same surface water sources. Also, information on methods of risk reduction against the uncertainty of oral exposure to human health is limited.

**UTILIZATION OF CYANOBACTERIA**

In addition to the dangers of microcystin produced by Cyanobacteria previously discussed, Cyanobacteria attracts more and more attention to the production of some valuable...
products (Axmann et al., 2014). It is necessary to explore the possibility of adopting environmentally friendly applications of cyanobacteria in the provision of worldwide solutions in the aspect of mitigating the energy crisis, alleviating the problem of plastic, solving the waste and wastewater problems, as well as the clean production. The diverse, ubiquitous and easily available in nature, make cyanobacteria potentially being a suitable candidate for various purposes (Deviram et al., 2020).

Several studies have been conducted to improve the benefits of cyanobacteria to human life. These bacteria have proven their possible roles in the world, in providing clean and sustainable energy, also other valuable products include food (Sathasivam et al., 2019), dietary supplements (Costa et al., 2019; Scoglio, 2018), high-value chemical products (Case & Atsumi, 2016), medicines (Noreña-Caro & Benton, 2018; Sathasivam et al., 2019), bioenergy (Aoki et al., 2018; Deviram et al., 2020; Quiroz-Arita et al., 2017), bioplastics, and wastewater treatment (Abdel-Raouf et al., 2012; Deviram et al., 2020; Subashchandrabose et al., 2013). However, an experiment tested into mice that had been dietary fed for 6 months with the AFA Klamath blue-green algae, resulted in excellent health with the liver in perfect condition (Clark et al., 2017). This study, further suggested the absence of an indirect relationship between the use of cyanobacteria and the ingestion route of exposure for humans.

Large scale application of cyanobacterial biofactory is still a technical challenge because of the yields and the omnmodification of products. However, the development of a feasible cyanobacterial biofactory can be enhanced through synthetic biology efforts, relying on the natural ability of cyanobacteria to synthesize carbohydrates and peptide (Noreña-Caro & Benton, 2018). Therefore, the further study of the harvesting and extracting, the environmental and economic feasibility, and also the development characterization methods for the physical properties and chemical composition of cyanobacteria utilization result products are necessary.

In the current progress, the use of cyanobacteria is for wastewater treatment and remediation of polluted environment. The use of cyanobacteria is still rarely found in scientific research, and is limited to wastewater with high concentrations of phosphate and nitrate (Gothalwal & Chilla, 2013). It was reported the cadmium deconcentration method by Nostoc calcicola cyanobacterium (Zhao et al., 2015), which can be applied to remediate the environment contaminated with other metals (Mani & Kumar, 2014; Yin et al., 2012). In the future, waste treatment and phytoremediation using cyanobacteria are expected to receive more attention. Especially is the implementation of biodiversity (Mangkoedihardjo & Samudro, 2014; Samudro & Mangkoedihardjo, 2020) both among microorganisms and between living organisms.

**CONCLUSION**

Although some applications are currently under debate due to the concern about the toxin accumulation in processed products such as food and dietary supplements. However, the use of cyanobacteria is prospective for environmental quality improvement. Cyanobacteria can be used for wastewater treatment and restoration of polluted environments. In-depth research is certainly needed to make effective use of it.

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