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Understanding the environmental roles of herbicides on cyanobacteria, cyanotoxins, and cyanoHABs

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Abstract Agrochemicals such as herbicides change the physical and chemical conditions of aquatic ecosystems and alter the community structure and dynamics of phytoplankton. Cyanobacteria are photosynthetic organisms found at the base of aquatic food chains. When cyanobacteria form blooms and produce toxins, they harm humans and the environment. Herbicides contaminate the aquatic environment when they are leached and transported via surface runoff from farms and industries. In this review, we show that these compounds have different mechanisms of action, but at high concentrations, they cause oxidative stress, interfere with the normal functioning of enzymes, and change the metabolic profile of microalgae and cyanobacteria. This paper demonstrates that at environmentally relevant concentrations, some herbicides facilitate the formation of cyanobacterial harmful algal blooms (cyanoHABs). The formation of blooms is driven by the tolerance of cyanobacteria to herbicides, where some of these compounds are degraded and converted into non-toxic forms. The degradation by-products are also used as a source of nutrients to support cyanobacterial growth. This adaptation sometimes leads to higher concentrations of bioactive compounds such as cyanotoxins in the aquatic environment. The increased levels of cyanotoxins and herbicides in water bodies can trigger a cascading toxicological effect on non-targeted organisms and the aquatic food chain. Despite the evidence confirming herbicides influence the growth of cyanobacteria and alter the structure of the phytoplankton community toward the formation of cyanoHABs, there is a lot that remains to be done to fully understand their impact on these organisms.

Keywords Herbicides · Cyanobacteria · Agrochemicals · Harmful algal blooms

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Introduction

Water is a valuable resource that is required to maintain life, but the provision of sufficient clean water for human use is a significant challenge worldwide (Tundisi and Tundisi 2016). Increasing human population causes severe food and water supply problems. The improper disposal of waste that is generated by human activities usually end up contaminating most aquatic ecosystems. Domestic, industrial, and agricultural wastes are the main sources of pollution of water bodies (WWAP 2015). Among these sources, agricultural activities pollute aquatic environments via the leaching of a substantial amount of agrochemicals, organic matter, drug residues, sediments, and saline drainage from farms into water bodies (UNEP 2016).

Pesticides comprise a diverse range of chemical agents, such as herbicides, insecticides, fungicides, among others. Any substance, be it pure, a blend, or as a cocktail, intended to prevent, destroy or mitigate pests of animal or plant species which may affect the productivity, processing, and marketing of agricultural products is a pesticide (EPA 2009; FAO 2015).

The use of pesticides began in the 19th century and is divided into three phases (Zhang et al. 2011a). The first phase began before 1870 and was marked by the use of natural pesticides. For example, in ancient Greece, sulfur was used to control pests. In the second phase, between 1870 and 1945, the use of synthetic inorganic pesticides began. The third phase, from 1945, was the era of synthetic organic or organic pesticides such as 2,4-D and DDT. The beginning of the third phase ended the use of natural pesticides but promoted the use of synthetic pesticides, also known as chemical pesticides (Zhang et al. 2011a). The 1990s came with a warning on the risks of chiral pesticides that acted on target and non-target species, constituting both environmental and human health risks (Drăghici et al. 2013; de Albuquerque et al. 2018).

Pesticides have toxic components that can have acute, sub-acute, and chronic effects on human and environmental health (Zhang et al. 2011a). Acute intoxication causes human mortality worldwide, especially in developing countries, due to the precarious or non-existent protective equipment for farmers during the manipulation and application of hazardous pesticide formulations (Mateo-sagasta and Turral 2017). Exposure to pesticides can cause infant mortality (Cremonese et al. 2014), Alzheimer's disease (Hayden et al. 2010), cancer (VoPham et al. 2015), and other life-threatening conditions (Mostafalou and Abdollahi 2017). Agrochemicals like herbicides adversely affect biodiversity in the aquatic environment, due to the amount used by farmers, this in most cases is directly proportional to the amount transported via surface runoff or leaching (Rocha et al. 2018).

There has been a considerable increase in pesticide use in recent decades, with global herbicide consumption estimated to rise to 3.5 million tonnes in 2020, and this increase correlates with the intensification of agricultural activity to feed the rising human population (Sharma et al. 2019a). The world population is projected to reach 9.8 billion by 2050 (UNDESA 2017). Unfortunately, higher agricultural productivity means higher use of pesticides to match the need of the increasing human population (De Albuquerque et al. 2018). At the moment, China is the world's leading consumer of pesticides, consuming 1.8×10^6 tonnes of pesticides per year, followed by the USA, France, and Brazil, with 7.6×10^4 tonnes of pesticides per year (WORLDATLAS 2017; Zhang et al. 2011a). In Australia, and North America, the use of pesticides is driven by the high cost of labor (Sharma et al. 2019a, b). Herbicides constitute 86% in Argentina and 56.1% in Brazil, of the pesticides used for various agricultural purposes (CASAFE 2013; SINDAG 2012).

The balance of aquatic ecosystems could be altered when contaminated by herbicides, selectively supporting the disproportionate proliferation of cyanobacteria, and the formation of cyanobacterial harmful algal blooms (cyanoHABs) (Mateo-sagasta and Turral 2017). Despite the potential toxicological impact of herbicides on the environment, there are very few reviews that explain the dynamics of cyanobacteria concerning how they alter the physiology, development, and community structure of aquatic ecosystems following the formation of cyanoHABs (Wong 2000; Tsui and Chu 2003; van Wijngaarden and Arts 2018).

Herbicides

The term herbicide can be used to define substances or pesticides used to control weeds in agriculture (Kim et al. 2017). Herbicides are prepared to have a direct effect on plants via a variety of biochemical reactions that lead to the inhibition of photosynthesis, nitrogen fixation, and growth (Kim et al. 2017; Altman and Altman 2018). 2-methyl-4-chlorophenoxyacetic acid, a synthetic auxin, was the first herbicide produced during World War II, and this compound is the first organic compound industrially produced (Heap 2014). Over the past 65 years, chemical companies have introduced more than 300 herbicidal active ingredients to the market (Duke 1990; Graymore et al. 2001; Lipok et al. 2009; Heap 2014; Ahmad 2017; Gupta 2018).

Herbicides are classified based on their mechanism of action and their toxicity. The Global Herbicide Resistance Action Committee (HRAC), categorizes herbicides by their mechanism of action because they interfere with the biosynthesis of plant components such as pigment, lipids, and amino acids. Herbicides lyse plant cell membranes, inhibit growth and development, and inhibit the normal functioning of enzymes and metabolic pathways (Altman and Altman 2018). According to the HRAC classification, the main chemical families of herbicides include carbamate, cyclohexanedione, glycine, pyridine, sulfonylurea, triazines, among others (Beffa et al. 2019). Among these chemical families, triazines block photosystem II (PS II); cyclohexanedione which inhibits acetyl-CoA carboxylase; sulfonylaminocarbonyl–triazolinone that interrupts the synthesis of acetolactate; and thiocarbamate that disrupts lipid and amino acid synthesis (Duke 1990; Beffa et al. 2019).

Regarding the classification based on toxicity, herbicides, like chemicals, can be classified according to the Globally Harmonized System (GHS) of classification and labeling of chemical products, which is recommended by the United Nations Conference on Environment and Development (GHS 2009). The classification of these substances falls under the ’Dangerous to the aquatic environment—Acute’ and the ’Dangerous to the aquatic environment—Chronic’. The basic elements used for this classification are Acute aquatic toxicity, Chronic aquatic toxicity, Potential or Actual bioaccumulation, and Degradation (biotic or abiotic) of chemical products (GHS 2009). The classification proposed by the GHS serves as a guide for data obtained using the Organization for Economic Cooperation and Development (OECD) Test Guidelines. These common global systems of classification are necessary to avoid contradictions and errors in the classification and definition of the different chemical classes of herbicides (Beffa et al. 2019) (Fig. 1).

Herbicides constitute about 47% of the global agrochemical market (Sharma et al. 2019a, b), with glyphosate being the most widely used and sold in more than 100 countries in Africa, Asia, North America, and Southern America (Fig. 2) (Williams et al. 2000; Zhou et al. 2020). In contrast to what occurs in other regions, the European Union has reduced its trade in several herbicides (Zhang et al. 2011a, b), and even banned or restricted the use of herbicides like glyphosate (Van et al. 2018). Also, herbicides are increasingly being adopted in developing countries with labor shortage problems and the need to increase crop yield (Gianessi 2013). According to Sharma et al. (2019a, b), as the human population continues to increase, so will the demand for food, leading to higher use of herbicides than the already worrisome present-day high levels. The intensive use of herbicides contaminates aquatic ecosystems by bioaccumulating in biological matrices (Xia 2005; Tsui and Chu 2008; Candela et al. 2010; Wu et al. 2016), thus, adversely affecting non-target species such as cyanobacteria (Arunakumara et al. 2013; Candela et al. 2010; Chen et al. 2007; Wu et al. 2016).

Cyanobacteria

Cyanobacteria or blue green algae are photosynthetic prokaryotes (Whitton 1992) with uni- or pluricellular forms (colonies and filaments) (Stewart 1980). They are distributed in different environments with sufficient moisture content and are dated from the Pre-Cambrian period (Farquhar et al. 2000). These organisms are a component of the phytoplankton community and are key constituents of the food chain in aquatic ecosystems (Bozelli and Huszar 2003). The physical, chemical, and biological characteristics of water shape the community of cyanobacteria (Tundisi et al. 2008). The eutrophication of lacustrine environments coupled with changing global climate and the presence of herbicides causes the formation of blooms of cyanobacteria (Carmichael and Falconer 1993). Cyanobacterial blooms alter water quality in terms of odor, color, flavor, and availability. Potential toxin-producing cyanobacteria biosynthesize and release toxins into the environment, and their excessive proliferation makes water treatment difficult and very expensive (Carmichael and Falconer 1993; Chia et al. 2017).

Cyanobacteria produce toxins called cyanotoxins, which are secondary metabolites that are produced as by-products or final products of metabolic reactions. These toxins are often released into the environment. They intoxicate aquatic and domestic animals

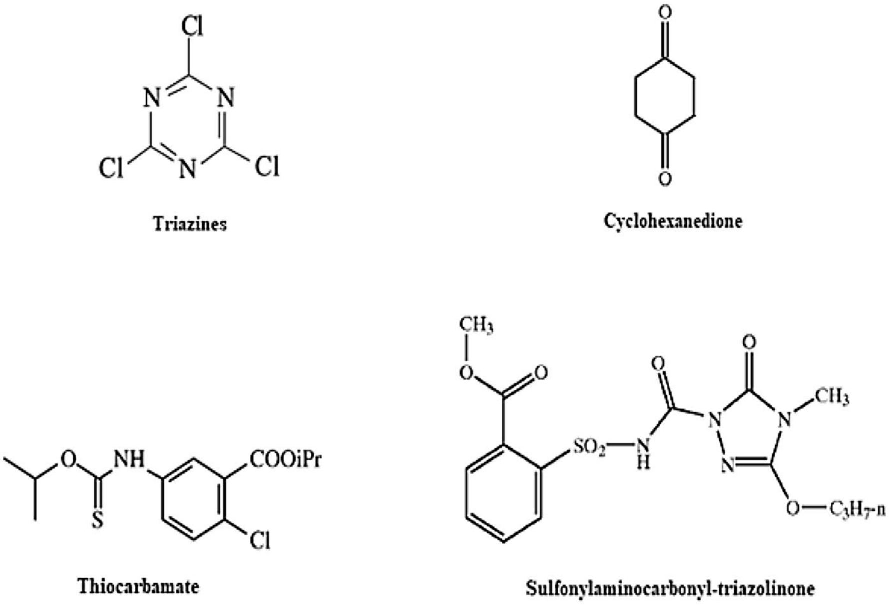

Fig. 1 Examples of chemical structures of herbicides belonging to the triazines, cyclohexanedione, thiocarbamate, and sulfonylaminocarbonyl–triazolinone classes

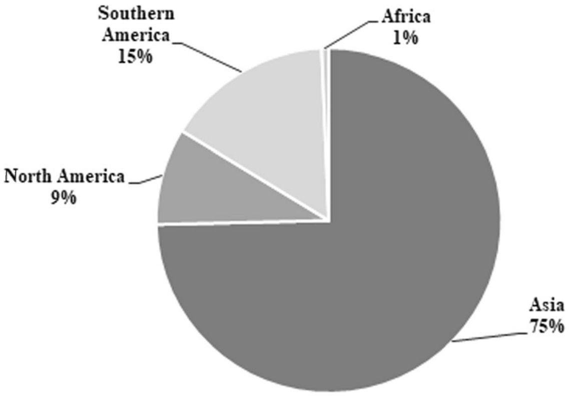

Fig. 2 Herbicide use in Asia, North America, South America, and Africa. (FAO 2019)

(Carmichael et al. 2001) and humans (Jochimsen et al. 1998). According to their mechanism of action, cyanotoxins are classified as neurotoxins, hepatotoxins, cytotoxins, and dermatotoxins (Chia et al. 2017). The biological and ecological role of cyanotoxins is not yet fully understood, but there are inferences that some are also allelochemicals with essential roles in shaping phytoplankton community structure and successional processes (Chia et al. 2018). Also, the production of cyanotoxins can be an act of defense against predation (Pineda-Mendoza et al. 2014).

Occurrences of toxic cyanobacteria have been reported in several regions of the world. The most intense impact of cyanotoxins has been recorded in communities of large-scale agriculture in Asia, Central and South America, Africa, Australia (New Zealand), and the Pacific Basin (Paerl et al. 2018). Some regions of China have reported cases of liver cancer in humans exposed to cyanotoxins (Ueno et al. 1996). The first documented case of human intoxication by cyanotoxins occurred in Brazil in 1996 in a hemodialysis clinic (Jochimsen et al. 1998).

Growth, photosynthetic effects and nitrogen fixation of cyanobacteria exposed to herbicides

Herbicides are prepared to have a direct effect on plants by influencing a variety of biochemical reactions (Altman et al. 2018). Studies on the effect of herbicides on the physiology and development of cyanobacteria generally begin with the evaluation of growth response (Wong 2000; Tsui and Chu 2003; van Wijngaarden and Arts 2018). For example, the findings of Du et al. (2017) demonstrated significant growth stimulation of *Microcystis aeruginosa* and *Microcystis viridis* exposed to low concentrations of fenoxaprop-p-ethyl. High concentrations of glyphosate inhibited the growth of cyanobacteria, and the changes in growth correlated positively with changes in pigment quality and quantity (Kreitlow et al. 1999; Saxton et al. 2011; Liu et al. 2014; Wu et al. 2016; De Stefano et al. 2018). This correlation is due to the critical role pigments play in the uptake and transfer of energy during photosynthesis. Therefore, the inhibition of chlorophyll biosynthesis leads to stunted cyanobacterial growth (Wu et al. 2016). Abou-Waly et al. (1991) and Peterson et al. (1994) observed the adverse effects of high concentrations of atrazine, hexazinone, and diquat on *Microcystis, Pseudoanabaena, Anabaena, Oscillatoria,* and *Aphanizomenon*. Ye et al. (2013) and Nyström et al. (1999) confirmed the inhibition of the growth of phytoplankton when exposed to diclofop and sulfonylurea. These studies reveal that depending on the type of herbicide, exposure concentration, exposure duration, and cyanobacterial species/strain, the influence of herbicides on cyanobacterial growth may vary (Nyström et al. 1999; Aslim and Ozturk 2009; Shen and Luo 2011; Ye et al. 2013). For example, Aslim and Ozturk (2009) revealed that the EC50, the concentration causing a 50% reduction in cyanobacterial growth, of different herbicides ranged from 50–200 mg l^{-1}. These authors found that the severity of the toxicity of several herbicides became more pronounced as the duration of exposure prolonged. Also, among the ten isolates Aslim and Ozturk (2009) investigated, *Microcystis* sp. S_{17} and *Synechococcus* sp. S_{24} were the most sensitive to trifluralin, 2,4-D, and linuron.

Cyanobacteria perform oxygenic photosynthesis where water is used as an electron source, and this process leads to the generation of oxygen, which is released into the atmosphere (Soo et al. 2017). Some herbicides are competitive inhibitors of cyanobacterial photosynthetic proteins as they disrupt the process of organic substrate production during photosynthesis. The efficiency of photosystem II (PSII) is significantly reduced by herbicides (Lürling and Roessink 2006). Herbicides target the PSII and compete with plastoquinone (an electron acceptor) form binding at the plastoquinone QB site in the D1 subunit of the protein (Fig. 3). Consequently, the transfer of electrons from plastoquinones QA to QB is blocked (Broser et al. 2011). Herbicides such as Terbutryn and others that target PSII alter the redox potential of QA, leading to photoinhibition.

Mutation studies of cyanobacteria with natural resistance to herbicides reveal the role of amino acid substitution of phenylalanine to serine, or valine to isoleucine in the D1 protein by point mutations at codons 211 and 219 of the *psb*A1 coding locus, respectively (Hirschberg et al. 1987; Gingrich et al. 1988; Ajlani et al. 1989; Ohad and Hirschberg 1990). The D1 is the QB-binding protein and these mutations confer resistance to herbicides (Gingrich et al. 1988). However, there are differences in the binding of different herbicides to PSII. Specifically, phenolic herbicides tend to bind endothermically, leading to the destabilization of PSII core complex (PSIIcc), while triazines and urea-type herbicides have a negative binding enthalpy, which stabilizes the complex (Broser et al. 2011). Beyond the individual effects of herbicides, they tend to compete for herbicide binding sites when they simultaneously occur in aquatic ecosystems. Allen et al. (1983) showed that radiolabeled atrazine and unlabeled diuron competed for the same binding site in *Aphanocapsa.* Some studies showed that herbicides influence the redox properties of QA (Krieger-Liszkay and Rutherford 1998; Rutherford and Krieger-Liszkay 2001), by either increasing (urea-type herbicide) or decreasing (phenolic herbicides) potentials (Broser et al. 2011).

There is an assumption that with sufficient levels of P and Fe in the aquatic environment, nitrogen fixation is expected to supply the N deficit. On the contrary, it is difficult to find this stoichiometric relationship as changes in environmental factors and the presence of pollutants (e.g., herbicides) limit this process in the aquatic ecosystem (Paerl 1990, 2017; Paerl et al. 2016). Some studies demonstrate that increasing concentrations of herbicides adversely affect nitrogen fixation in cyanobacteria such as *Nostoc* spp., *Anabaena* spp, and *Nostocpaludosum,* (Mishra and Pandey 1989; Irisarri et al. 2001; Shinde 2018). A brief background on the process of nitrogen fixation is important to understand how herbicides affect this process. Filamentous cyanobacteria fix atmospheric nitrogen using specialized cells called heterocysts, while non-heterocystous cyanobacteria use vegetative cells to perform nitrogen fixation with nitrogenase to produce ammonia (NH_3) to support aquatic fertility (Leganés and Fernández-Valiente 1992; Jarvie et al. 2018). Nitrogenase is an enzyme complex containing a dimeric Fe-protein called dinitrogenase reductase, which conveys electrons to the tetrameric MoFe-protein. The MoFe-protein converts nitrogen molecules to ammonia (Fig. 4). Nitrogen fixation requires

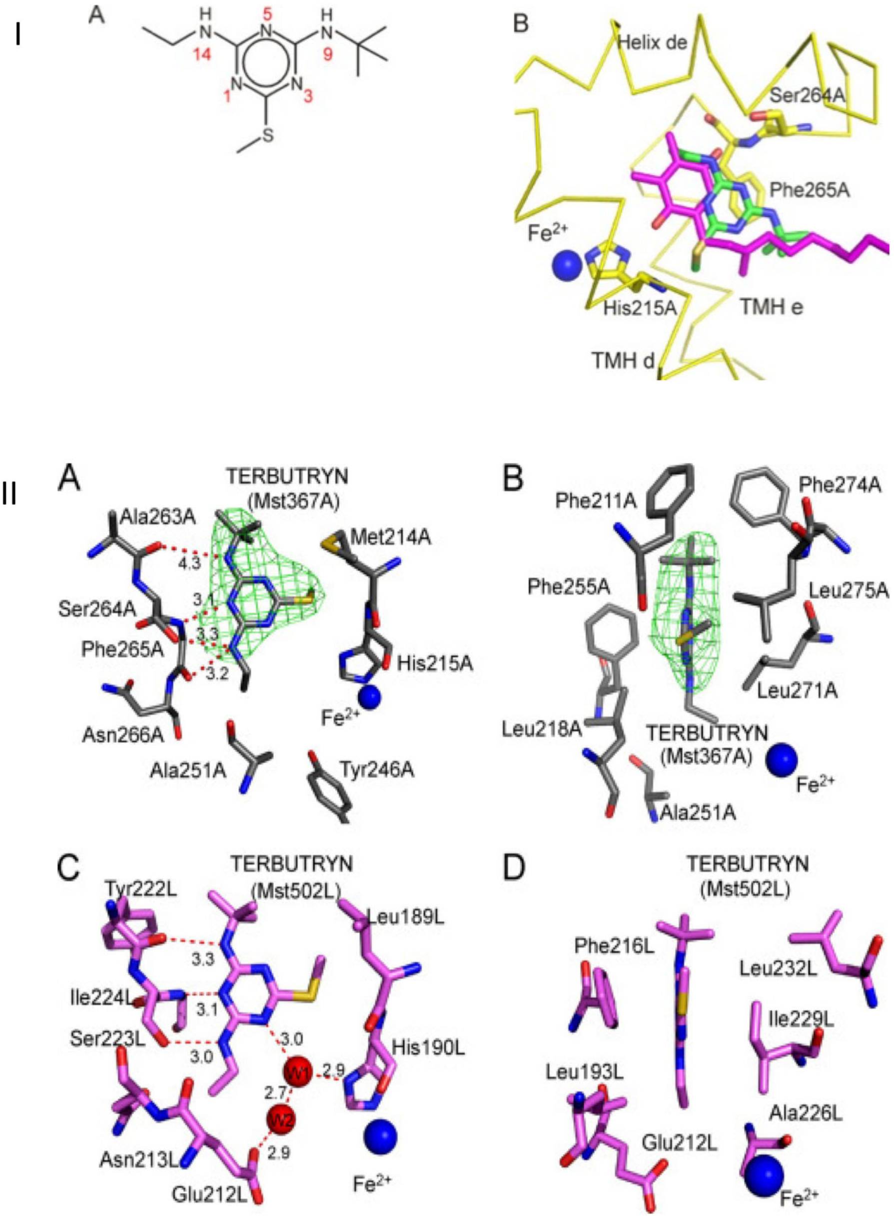

Fig. 3 Inhibition of Photosystem II by the herbicide terbutryn. I. Plastoquinone and terbutryn binding in PSIIcc. I.A, the structural formula of terbutryn. I.B, superposition of structural models with plastoquinone or terbutryn linked to the Q_B site. II.A, B Terbutryn bound to the *T. elongatus* PSIIcc Q_B site or *B. viridis* pbRC as derived from 3.2 Å crystalline structures (PDB codes 3PRQ and 3PRR) and 2.0 Å resolution (PDB code 1DXR (25)), respectively. For each RC, two orientations are shown, visualizing (**a** and **c**) or along (**b** and **d**) the plane of the terbutryn ring. Terbutryn and amino acid residues surrounding the D1 (Psbcc PSbcc) or L (pbRC) subunit are shown, and possible hydrogen bonds linking the protein to the herbicide are displayed as dashed lines (distances are given in Å). For PSIIcc (A and B), the electronic density of terbutryn is shown as a mesh at a contour level of 1.2. The non-heme iron cofactor and two water molecules (W1 and W2) are represented as spheres. Source: Broser et al. (2011, p.15967–15,968)

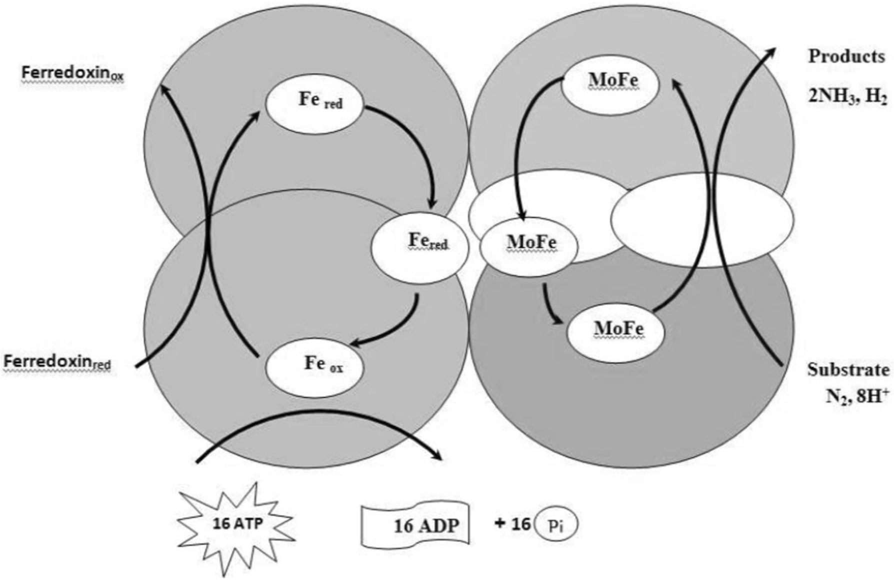

Fig. 4 The structure of nitrogenase (Issa et al. 2014). Abbreviations: Fe, dimeric Fe-protein; MoFe, tetrameric MoFe-protein; ox, oxidized; red, reduced; N_2, Nitrogen molecule; NH_3, ammonia; H_2, hydrogen molecule

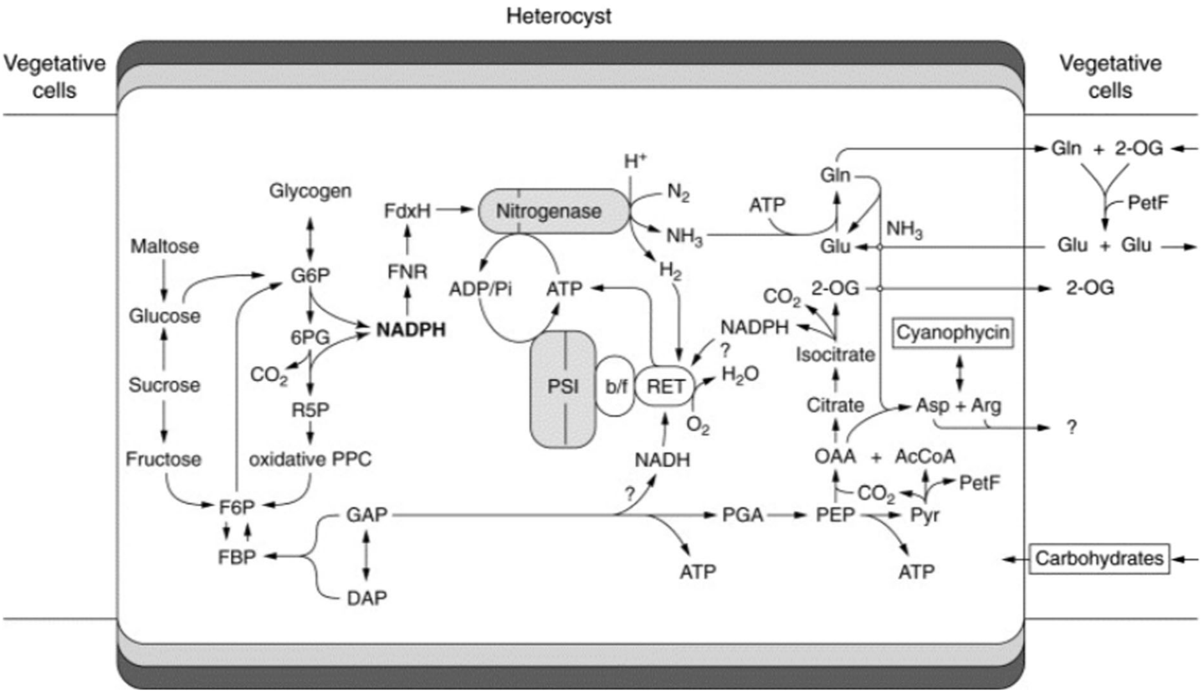

Fig. 5 Process of nitrogen fixation by heterocystous cyanobacteria. The figure reveals the interactions between photosynthetic products, nitrogen fixation, and the production of ammonia by nitrogenase. AcCoA, acetyl coenzyme A; Arg, arginine; Asp, aspartate; b/f, cytochrome b6f complex; F6P, fructose 6-phosphate; PetF, vegetative cell type ferredoxin; Glu, glutamate; Gln, glutamine; OAA, oxaloacetate; 2-OG, 2-oxoglutarate; 6PG, 6-phosphogluconate; PGA, 3-phosphoglycerate; Pi, inorganic phosphate; R5P, ribose 5-phosphate. (Böhme 1998; Issa et al. 2014)

an anaerobic environment, ATP, and a reducing power source (Fig. 5). The heterocysts produce ATP via cyclic photophosphorylation, whereas the vegetative cells provide the carbon compounds needed to drive the process (Fig. 5) (Gallon 2001).

The exact mechanism of action of herbicide inhibition or stimulation of nitrogen fixation is not currently well-understood but available evidence reveals a close relationship with photosynthesis and the generation of reactive oxygen species (ROS). For nitrogen fixation to proceed, heterocysts obtain carbohydrates from the vegetative cells of diazotrophic cyanobacteria, while glutamine is moved from heterocysts to vegetative cells. The presence of sufficient quantities of substrates such as glycogen, sucrose, fructose, glycolytic substrates (e.g., pyruvate), and intermediates of the oxidative pentose-phosphate cycle (e.g., glyceraldehyde 3-phosphate) support nitrogenase activity in heterocystous cyanobacteria (Issa et al. 2014). The inhibition of nitrogen fixation by herbicide comes mainly by the inhibition of photosynthesis that results in lowered carbon substrates, and increased intracellular ROS content further inhibits this process (Leganés and Fernández-Valiente 1992). Also, herbicide-induced variations in the ratios of intracellular carbon to nitrogen, control the redox levels of the secondary quinone acceptor, QB, causing the impairment of electron transfer between QA and QB (Berman-Frank et al. 2003), which can have a cascading effect on the overall success of nitrogen fixation. This process is critical because it directs energy transfer from the phycobilisomes to photosystem I (PSI) as nitrogen fixation progresses.

Chia et al. (2018) demonstrated that nitrogen fixation by diazotrophic cyanobacteria (*Anabaena, Trichodesmus,* and *Dolichospermum*) is significantly inhibited by stressful conditions that lead to oxidative stress. Increasing levels of ROS cause a rapid reduction in nitrogenase activity by altering the protein structure and inhibiting the synthesis of nitrogenase in nitrogen-fixing cyanobacteria (Berman-Frank et al. 2003; Bothe et al. 2010). The influence of herbicides varies between species, for example, while butachlor and fluchloralin inhibit nitrogen fixation in *Nostoc muscorum,* the reverse happens to *Gloeocapsa* sp (Singh and Tiwari 1988). These differences are tied to different adaptations to nitrogen fixation to protect against increase intracellular ROS or O_2. For example, *Trichodesmium* protects itself against increasing ROS by using a complex interaction between the spatial and temporal segregation of the photosynthetic, nitrogen fixation, and respiratory processes (Berman-Frank et al. 2003). The circadian clock regulates the expressions of genes that are related to the biosynthesis of nitrogenase and photosynthesis to activate PSI and PSII. Thus, photosynthetic genes such as *psaA* and *psbA* undergo a temporal difference with nitrogen-fixing genes such as *nifHDK* (Chen et al. 1999). These physiological and gene expression changes are influenced by herbicides and other pollutants, and collectively, they influence the availability and speciation of nitrogen in aquatic ecosystems and the growth of sensitive species.

Tolerance, biotic interactions, cyanotoxins, and blooms formation of cyanobacteria exposed to herbicides

Eutrophied waterbodies are frequently plagued with cyanobacterial blooms, which constitutes a threat to the environment and human health (Havens 2008; Zhang et al. 2017). Several studies have shown that nutrient conditions, light quality, temperature, and other hydrological conditions influence the successional processes of phytoplankton species (Paerl and Huisman 2008; Davis et al. 2009; Paerl and Paul 2012; IPCC 2018). Also, biological conditions such as competition, predation, and allelopathy tend to alter the successional processes of phytoplankton species towards the formation of cyanobacterial blooms (Chia et al. 2018). However, there is a paucity of information on the influence of herbicides on successional processes between phytoplankton species and the formation of cyanoHABs. Herbicides are indiscriminately released into the aquatic environment by increasing agricultural activities, a situation that exposes cyanobacteria to them. Herbicides can also alter the composition and diversity of the phytoplankton community (Pesce et al. 2009), causing changes in algae metabolism and promoting oxidative stress (Romero et al. 2011; Chen et al. 2012).

The environmental risks of herbicides are increased during the farming season and high rainfall because surface runoff, leaching, and accidental spills lead to higher herbicide concentrations in the aquatic ecosystem (Clair et al. 2012; Masiá et al. 2013). To demonstrate how herbicides affect successional processes of phytoplankton communities, Lürling and Roessink (2006) demonstrated that metribuzin reversed the competitive advantage of *Scenedesmus* over *Microcystis,* favoring the dominance of the latter. These authors revealed that herbicides that inhibit photosynthesis may not only alter algal community structure but will furnish founder populations of cyanobacteria with the opportunity to become dominant and form cyanoHABs. Compared to other phytoplankton and aquatic macrophytes, cyanobacteria are resistant to environmentally relevant concentrations of herbicides (Forlani et al. 2008; Harris and Smith 2016; Richardson et al. 2016; Brêda-Alves et al. 2020). The tolerance or resistance of cyanobacteria to herbicides is influenced by prevailing physicochemical conditions like nutrient levels of the aquatic medium. For example, Brêda-Alves et al. (2020) found that nutrient (nitrogen and phosphorus) enrichment enhances the tolerance of *M. aeruginosa* and *R. raciborksii* to clethodim. In addition to conditions that selectively favor founder populations during succession, predation, competition, and changes in nutrient regimes, herbicides may promote the formation of cyanobacterial blooms at the disadvantage of other competing species. This is tied to the tolerance or resistance of cyanobacteria to triazine and other types of herbicides, and the competitive advantage the herbicides confer on cyanobacteria (Maule and Wright 1984; Lürling and Roessink 2006). The vulnerability of other algal types (chlorophytes and diatoms) to herbicides changes the composition of the phytoplankton community toward the dominance of cyanobacteria, a group that is less palatable to zooplankton (Lürling and van der Grinten 2003; dos Santos Severiano et al. 2018). Thus, herbicides not only change the composition of phytoplankton in aquatic ecosystems, but also, alter the quality and quantity of food available to large-bodied zooplankton.

The tolerance of cyanobacteria to non-selective herbicides such as glyphosate to millimolar levels has been linked to various biochemical changes. Some cyanobacteria employ the insensitive 5-enol-pyruvyl-shikimate-3-phosphate synthase, as a target for glyphosate (Powell et al. 1991; Forlani et al. 2008). The enzyme belongs to the shikimate pathway. Other cyanobacteria breakdown herbicides and use the products as a nutrient source for growth (Forlani et al. 2008; Brêda-Alves et al. 2020). For example, the degradation of clethodim yields nitrogenous compound(s) from the N-oxo-sulfamoyl chloride, contributing to the levels of nitrogen in the aquatic medium. Elanskaya et al. (1998) demonstrated that *Synechocystis* sp. modified dinoseb to a non-toxic product with a similar absorption spectrum to that of dithionite treated dinoseb having reduced nitro-groups. Also, several cyanobacteria use phosphonate groups in glyphosate as a phosphorus source (Forlani et al. 2008). Interestingly, the species that are unable to use phosphonate as a phosphorus source, metabolize glyphosate to forms that are less toxic to them. These demonstrate that several mechanisms are employed to confer herbicide tolerance to cyanobacteria. Forlani et al. (2008) suggest that glyphosate tolerance is restricted by low cell permeability to glyphosate. Also, phytoplankton tolerance to herbicides is significantly influenced by the levels of nutrients (Chia et al. 2016) as well as changes in other hydrological conditions (Irisarri et al. 2001; Chen et al. 2012). Exogenous addition of antioxidant enzymes such as superoxide dismutase (SOD) to culture medium alleviates the adverse effects of herbicides.

The induction of oxidative stress in phytoplankton by herbicides leads to the up-regulation of antioxidant enzyme activities. Some studies show that the activities of intracellularly synthesized antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), peroxidase (POD), and glutathione S-transferase (GST) are significantly altered in several phytoplankton species, as a function of exposure time and concentrations of herbicides (Chia et al. 2016; Wu et al. 2016; Du et al. 2017). Enzymes such as POD and CAT detoxify reactive oxygen species (ROS) like hydrogen peroxide (H_2O_2), superoxide (O_2^-), and hydroxide (HO-). They convert H_2O_2 to oxygen and water, thereby reducing the oxidative damage caused by these ROS. Superoxide Dismutase, on the other hand, acts primarily on the superoxide (O-) molecule, converting it H_2O_2, which is subsequently converted to O_2 and H_2O by CAT and POD. The phase II enzyme, GST, bio-transforms and detoxifies xenobiotics such as herbicides to forms that are less toxic to cyanobacteria and other photosynthetic microorganisms (Vestena et al. 2011). At environmentally relevant levels of herbicides detected in water (Mao et al. 2020), the growth and tolerance of harmful bloom-forming cyanobacteria such as *Microcystis, Raphidiopsis raciborskii* (*Cylindrospermopsis* *raciborskii*), *Pseudoanabaena*, *Anabaena*, *Oscillatoria*, and *Aphanizomenon* to herbicides have been linked to the up-regulation of the activities of antioxidant enzymes (Abou-Waly et al. 1991; Peterson et al. 1994; Ye et al. 2013; Wu et al. 2016; Brêda-Alves et al. 2020).

The presence of herbicides can also affect the production and release of cyanotoxins by cyanobacteria. These bioactive metabolites are stored within the cell of cyanobacteria but are released throughout the day via a circadian rhythm (Carneiro et al. 2009; Cordeiro-Araújo and Bittencourt-Oliveira 2013; D'Agostino et al. 2016) or by cell lysis (White et al. 2005). The effect of herbicides on cyanotoxin production and release by cyanobacteria has been poorly investigated, but it is clear that the agrochemicals alter the physicochemistry of water and are sometimes toxic to them (Liu et al. 2015; Wu et al. 2016). Hence, it is reasonable to hypothesize that herbicides will cause growth inhibition or sudden death of toxin-producing strains, which will lead to the release of cell-bound or particulate toxins. The death of cyanobacteria leads to a loss of their membrane integrity, which could lyse their cell and release cell-bound cyanotoxins. This case has been demonstrated in several studies on natural and laboratory populations of toxin-producing strains of cyanobacteria exposed to different toxicants (Liu et al. 2016). Specifically, the biosynthesis and extracellular release of these metabolites can be affected by the presence and levels of herbicides that damage cell membrane integrity. Wu et al. (2016) demonstrated that the oxidative stress caused by glyphosate damaged the cell membrane of *M. aeruginosa*, causing microcystins extravasation and increasing the levels of the metabolites in the environment. Brêda-Alves et al. (2020) also supported this finding by showing that clethodim exposure leads to lipid peroxidation—an indicator membrane lipid damage—and the loss of cell membrane integrity correlated positively with increased total cyanotoxins content of *M. aeruginosa* and *R. raciborskii.*

Among the few studies reporting the effects of herbicides on cyanobacterial toxins is the study by Brêda-Alves et al. (2020). In this work, the authors demonstrated that the herbicide increased the production of microcystins and saxitoxins by *Microcystis aeruginosa* and *Raphidiopsis raciborskii*, respectively. There is a positive relationship between cyanobacterial growth rate and cellular cyanotoxins content (Sevilla et al. 2010). Thus, the higher the risks of cyanoHABs formation in the presence of contaminants such as herbicides. Another aggravating factor that contributes to the formation of blooms is the degradation of herbicides in the aquatic environment. Vera et al. (2010) confirmed a significant increase in phosphorus concentration of an aquatic medium due to the degradation of Roundup® in mesocosm experiments. Consequently, there is an increase in phosphorus content eutrophies in the surrounding environment, which could lead to a higher cyanotoxins production and release by cyanobacteria (Chia et al. 2018).

The production of cyanotoxins, such as microcystin, is regulated non-ribosomally by multifunctional enzymes that contain polypeptide synthetase (PS) and polyketide synthase (PKS) modules (Nishizawa et al. 1999; Tillett et al. 2000). Agrochemicals can affect the cyanobacterial gene expression, changing the transcription levels of the *mcy*A and *mcy*D genes (Zhang et al. 2017). These genes form part of the microcystin LR, -RR gene complex and have been extensively described in the published literature (Nishizawa et al. 2000). Zhang et al. (2017) demonstrated that the production of microcystin by *Microcystis aeruginosa* increased in the presence of glufosinate, which correlated with the up-regulation of transcription levels of the *mcy*A genes. The up-regulation of the expression of *mcy* genes combined with growth stimulation and cyanoHABs formation can constitute a serious environmental risk (Zhou et al. 2013).

Conclusion

This review highlights the influence of herbicides on the growth and physiology of cyanobacteria. Specifically, toxin production, photosynthesis, and nitrogen fixation significantly affected the following exposure of cyanobacteria to herbicides. The effect of herbicides on cyanobacteria depends on exposure concentration and duration, and the species exposed. These findings imply herbicides may be playing a significant but underreported role in the aquatic environment. The use of omics techniques such as proteomics, transcriptomics, and metagenomics in laboratory and field studies will lead to a better understanding of the effects of herbicides on cyanobacteria community structure, dynamics, and ecosystem functions. Regardless, one thing is clear, environmentally relevant concentrations of herbicides influence different aspects of the ecology of cyanobacteria.

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