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REVIEW ARTICLE

PLANT-CYANOBACTERIA INTERACTION: PHYTOTOXICITY OF CYANOTOXINS

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SUMMARY

Cyanobacteria from freshwater and also from marine sources produce a wide array of toxic chemicals and secondary or bioactive metabolites. These are mainly nitrogen-rich alkaloids and peptides and are now identified as to pose threats both to human and environmental health as well as on aquatic and terrestrial plants. Irrigation of edible plants with Cyanobacteria containing water may pose threat of indirect exposure of human health to cyanotoxins via bio-accumulation of these toxins in plant tissues. Moreover, Cyanotoxins have been shown to inhibit plant growth and development. It has also been suggested that some of the compounds may have ecological roles as allelochemicals and can be used as potential biocides and even to combat malignant cells.

In this review, we highlight the different naturally occurring Cyanobacterial toxins popularly known as cyanotoxins and their interaction with plants with special emphasis on phytotoxic effects of cyanotoxins. Also, existing evidence for the positive taxis of plant-cyanobacteria interaction and potential for development and application of bioactive molecules from Cyanobacterial toxins are highlited.

Key words: Cyanobacteria, toxins, phytotoxicity, allelopathy, biocide

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1. Introduction

'Cyanobacteria', commonly known as 'blue-green algae', have been dwelling on the planet for billions of years. They are believed to be associated with increasing the atmosphere's oxygen levels to allow life on earth to exist. However, Cyanobacteria may overproduce in certain environments, leading to algal blooms. Many of these are harmful blooms and are known to be due to nitrogen and phosphorus fertilizer overflow in eutrophic water bodies. Looking at the fossil record to nearly 3.5 billion years ago, these Cyanobacteria are known to produce a large number of biologically active compounds specially those of nitrogen-rich alkaloids and peptides (Gerwick, 2001). These are now identified to pose threats both to human and environmental health as well as on aquatic and terrestrial plants worldwide. Irrigation of edible plants with Cyanobacteria-containing water may pose threat of indirect exposure of human health to cyanotoxins (Cyanotoxins) via bio-accumulation of these toxins in plant tissues. Moreover, Cyanotoxins have been shown to inhibit plant growth and development (Ko's *et al.* 1995). Although rare, phytotoxic effects of Cyanotoxins on terrestrial plants have got attention of researchers, showing physiological and morphological alterations by Cyanotoxins in a range of terrestrial plants (Chen *et al.*, 2004; Pflugmacher, *et al.*, 2007). Here, we will review the different naturally occurring Cyanobacterial toxins popularly known as Cyanotoxins and their interaction with plants with special emphasis on phytotoxic effects of Cyanotoxins. At the end, existing evidence for the plant-cyanobacteria interaction since time immemorial like beneficial symbiosis, cyanobacterial role in chloroplast evolution and potential for development and application of bioactive molecules from Cyanobacterial toxins are also highlited in short.

2. Cyanotoxins

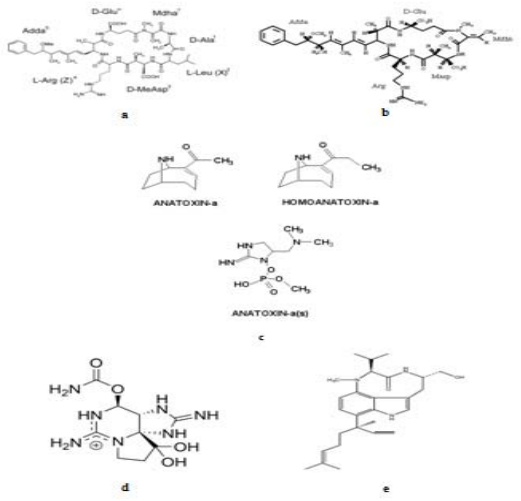
Cyanotoxins are a group of fatal toxic substances occuring in the cells of a number of Cyanophyceae (blue-green algae). Cyanotoxin forming genera occurring in freshwater includes *Microcystis, Anabaena, Planktothrix, Nostoc. Aphanizomenon* and *Cylindrospermopsis. Nodularia* is found predominantly in seawater (Zech, 2001). Broadly, Cyanotoxins may be divided into three main groups: hepatotoxins, neurotoxins, and cytotoxins (Codd, 2000). The hepatotoxins are generally cyclic oligopeptides which inhibit protein phosphatises and possess specific liver toxicity. About 100 variants of this class of substances have been identified and all contain a rare C20 amino acid "Adda". The toxicity of the algal nerve toxin is based on the fact that they either funtion as analogon of acetyl cholin (anatoxin-a), as cholin esterase inhibitor (anatoxin-a(S)) or that they block sodium channels (Saxitoxin) (Weller, 2002). The cytotoxins from cyanobacteria include aplysiatoxin, debromoaplysiatoxin and lyngbyatoxin A, B and C produced by the toxic cyanobacterium *Lyngbya*.

Hepatotoxins

These are the most commonly occurring toxins found in cyanobacteria and include the seven amino acid peptide microcystin (Fig.1a) and five amino acid peptide nodularin (Fig.1b) from *Microcystis aeruginosa* and *Nodularia spumigena* respectively (Burja *et al*., 2001). Microcystins (MCs), a group of hepatotoxin, are the most world-widely distributed Cyanotoxins produced also by other algal genera like, *Anabaena, Oscillatoria,* and *Nostoc* (Haider *et al*, 2003) and around 50 different variants of microcystins have been isolated from these species of cyanobacteria. Microcystins are cyclic heptapeptides with the general structure cyclo(-d-Ala-l-X-erythro-b-methyl-d-isoAspl-Y-Adda-d-isoGlu-*N*-methyldehydro-Ala. The aminoacid Adda (3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid) is considered responsible for the molecules' hepatotoxicity (Carmichael,1997). Microcystin-LR (MC-LR) is one of the predominant variant of MCs produced by cyanobacteria blooms (Sivonen and Jones, 1999).Microcystin-LR inhibits serine-threonine protein phosphatases 1 (PP1) and 2A (PP2A). Due to their effect on cytoskeleton, they are now used to study various cellular mechanismm(Honkanen *et al*, 1990).

Nodularin-R is a cyclic nonribosomal peptide produced by the planktonic cyanobacterium *Nodularia spumigena* (Sivonen *et al*., 1990). Nodularin-R is a heptapeptide and contains several unusual non-proteinogenic amino acids such as methyldehydrobutyrine and the β-amino acid ADDA *(all-S,all-E)*-3-Amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-diene acid). Nodularin-R is a cyanotoxin and poses a health risk for wild and domestic animals as well as humans. Nodularin-R is a potent hepatotoxin and may cause serious damage to the liver.

Fig1. Chemical structure of a: microcystins ; b: nodularin; c: anatoxins; d: saxitoxin and e: lyngbyatoxin A (Kaebernick and Neilan, 2001; Cardellina et al., 1979).



Neurotoxins

Algal neurotoxins specifically and selectively binds to the sodium channel in neural cells and prevents any sodium cation from going in or out of the cell. Since, neuronal transmittance of impulse and messages depends on depolarization of the cell, its affects a large nos of body function including breathing. As a result the diaphragm stops working and cardiorespiratory failure leads to death.

Kalkitoxin

Kalkitoxin a neurotoxin which blocks sodium channels preventing the nerves from transmitting their electrical signals. Kalkitoxin is a useful pharmaceutical compound and a valuable tool to understand the working of sodium channels and the effect of disease on them (Wu *et al*., 2000).

Antillatoxin

Lyngbya majuscula, a pantropical marine cyanobacterium is the source of antillatoxin (ATX), a structurally unusual lipopeptide (Orjala *et al,* 1995). Blooms of *L. majuscula* have been reported to cause respiratory irritation, eye inflammation, and severe contact dermatitis (Dennison *et al*., 1999). ATX has been shown to be among the most ichthyotoxic metabolites isolated till date from a marine microalga (Orjala *et al,* 1995) and has been demonstrated to be neurotoxic in primary cultures of rat cerebellar granule cells (Berman *et al*., 1999).

Barbamide

Barbamide was isolated from a Curaçao strain of Cyanobacterium *Lyngbya majuscula* and is known to be molluscicidal. Although it is a small molecule, barbamide has complex structural and biosynthetic features, including a trichloromethyl group and the methyl enol ether of a β-keto amide. The gene cluster of the *L. majuscula* producing barbamide has been reported in literature (Chang *et al*., 2002).

Anatoxins

The anatoxins are a group of neurotoxic alkaloids produced by a number of cyanobacterial genera including *Anabaena*, *Oscillatoria* and *Aphanizomenon*. The toxicity of these compounds (LD_{50}) varies from 20 μg kg^{-1} (by weight, I.P. mouse) for anatoxin-a(S) to 200-250 μg kg^{-1} for anatoxin-a and homoanatoxin-a, making them more toxic than many microcystins. Three different types of this toxins (Fig.1c) include Anatoxin-a, homoanatoxin-a and Anatoxin-a (s).

Anatoxin-a and homoanatoxin-a cause rapid death due to respiratory arrest (the mouse LD^sub 50^ is approximately 250 g/kg) (Devlin *et al,* 1977). Anatoxin-a (s) a unique phosphate ester of a cyclic N-hydroxyguanidine moiety and is a cholinesterase inhibitor (Mahmood and Carmichael, 1986, 1987).

Saxitoxin

Saxitoxin (Fig1d) is a neurotoxin naturally produced by certain species of marine dinoflagellates like *Alexandrium sp., Gymnodinium sp., Pyrodinium sp.* and cyanobacteria *Anabaena sp., Aphanizomenon* spp., *Cylindrospermopsis* sp. *Lyngbya* sp. *Planktothrix* sp. etc. (Clark *et al.,* 1999; Landsberg, 2002). Saxitoxin, one of the most potent natural toxins known and acts on the voltage-gated sodium channels of nerve cells, preventing normal cellular function and leading to paralysis. Saxitoxin is 1000 times more toxic than the potent nerve gas sarin.

Brevitoxins

Brevitoxins are neurotoxins produced by *Ptychodiscus brevis*, from which the name is derived. These are lipophilic compounds with a molecular weight of approximately 900 Da (Baden, 1989). Brevitoxin changes the threshold voltage at which sodium channel opening occurs, thus making the sodium channel for uncontrolled influx, and consequently, the affected nervous and muscular cells are hyperexcited.

Cytotoxin

The deadly cytotoxins from cyanobacteria include cytotoxic compounds such as, aplysiatoxin, debromoaplysiatoxin and lyngbyatoxin A (Fig.1e), B and C produced by the toxic cyanobacterium *Lyngbya*, which are filamentous

cyanobacteria abundant within tropical and subtropical waters.

3. Plant Cyanotoxin Interaction: Phytotoxicity

Effect of Cyanotoxin on Plant Seed germination rate

Seeds exposed to Cyanotoxins in scientific trials have been found to exhibit a lower germination rate than control groups. This may be due to the fact that exposure to Cyanobacteria aqueous extract may affect the metabolic activities of seeds during the germination process. However, resistance to Cyanotoxins varies with different plants. For example, rice seeds have been found to be more resistant than rape seeds (Chen *et al,* 2004). *Medicago sativa* showed inhibition of germination when exposed to cyanobacterial toxins (Microcystins and Anatoxin-a) and cyanobacterial cell-free crude extract (Pflugmacher *et al,* 2006) Reduction of germination rate was also observed in *Lens esculenta, Zea mays, Triticum durum* and *Pisum sativum* when exposed to MC-LR (Saqrane *et al.,*2008).

Effects of Cyanotoxins on seedlings growth and development

Plants are generally not killed by Cyanotoxins but plant growth may be inhibited **(**Mackintosh *et al.,* 1990) and result in a yield reduction. These effects have previously been reported by several authors (Crush *et al,* 2006; Ko´s *et al,* 1995; Pflugmacher *et al.,* 2006; Kurki-Helasmo *et al.,* 1998; McElhiney *et al.,* 2001).In most cases, effects on growth and leave and root development were recorded. For example, growth of potato (*Solanum tuberosum*) cultures were reduced at 0.005 mg/kg MC-LR in the a solid culture medium, and completely inhibited at 0.5–5 mg/kg MC-LR. Growth of bean (*Phaseolus vulgaris*) plants in culture was inhibited by MC-LR at 1.12 mg/kg (McElhiney *et al.,* 2001). A significant decrease in leaf and root lengths and in productivity of *Lepidium sativum* seedlings (Gehringer *et al.,* 2003) were caused by cyanobacteria MC-extract. These investigations suggest that exposure to Cyanotoxins through irrigation of cyanotoxin contaminated water can pose a threat to the quality and yield of crop plants.

Inhibition of Plant Regulatory Enzymes by Cyanotoxins

Cyanotoxins inhibit the action of regulatory enzymes called protein phosphates. Protein phosphates regulate nitrogen and carbon synthesis. Microcystin is a potent inhibitor of key regulatory enzymes (protein phosphatases) in both animals and plants. Protein phosphatases in plants regulate important cellular processes such as carbon and nitrogen metabolism, tissue development and photosynthesis. It has been shown that plant seedlings can take up microcystin (Abe *et al*., 1996; McElhiney, *et al*. 2001) inhibiting plant development, root growth and photosynthesis (Codd *et al.,* 1999; Chorus *et al*., 1999; Pflugmacher *et al,* 2006; Smith *et al*., 1994).

Cyanotoxins in Plant Cell Damage

Cell damage occurs as a result of cyanobacterial toxins. Necrotic lesions on leaves are also observed and likely due to microcystin-induced stress (Pflugmacher *et al.,* 2006). Plant exposure to microcystin results in the generation of reactive oxygen species such as hydrogen peroxide, and if the plant's antioxidant capacity is plagued then the cells die. Plants can detoxify microcystin but no studies have been performed to determine the length of time necessary to completely break down the toxin.

Phytotoxicity of Cyanotoxin: Potent human health risk

Cyanobacterial toxin uptake by crop plants occurs when irrigation is done with cyanobacteria containing water. Cyanobacterial toxins are phytotoxic. This means that they are toxic to and can induce negative responses in plants. When these are accumulated in crop plants it poses serious human health risk when they enter the food chain (Kurki-Helasmo *et al.,* 1998; McElhiney *et al.,* 2001; Codd *et al.,* 1999) Crop are able to store Cyanotoxins in sufficient concentration to induce morphological and physiological changes (Chen *et al*., 2004; Pflugmacher *et al*., 2006; Gehringer *et al*., 2003). Irrigation with water contaminated with *Microcystis* in *Lactuca sativa, Oryza sativa* and *Brassica napus* showed cells of cyanobacterium stuck to plant surface many days after irrigation

(Chen *et al.,* 2004; Codd *et al.,* 1999). However, *Brassica napus* shoots stored more microcystins than *Oryza sativa*, indicating that different plant species accumulate microcystins at different levels. There are reports regarding the translocation of MC within crop plants e.g. *Medicago sativa* L., *Triticum aestivum* L., *Cicer arietinum* L. (Chen *et al.,* 2004) *Brassica oleracea* var. *italica* and *Sinapis alba*(Järvenpää *et al.,* 2007). Roots of different plants are known to accumulate different concentration of microcystins e.g. clover (1.45 mg/kg DW), lettuce (0.68 mg/kg DW) and rape (0.12 mg/kg DW).

These results show that irrigation with microcystins containing water can move microcystins into animal and human food chain causing serious threat to the human kind. Special attention should be given to the presence MCs in crop plants and its degree of accumulation so as to take special care in avoiding their contamination in human food stuff. The above mentioned research on the phytotoxicity of cyanobacterial toxins are preliminary ones. More research needs to be performed to learn how to counter phytotoxic effects on food crops.

4. Positive taxis of Cyanobacteria towards the plant partners

The Cyanobacteria or blue-green algae are prokaryotic, photosynthetic microorganisms. They can be considered as a renewable biomass resource as the secondary metabolites released by them are mineralized by microflora to add to the soil mineral resources. To tell about the direct positive interaction of Cyanobacteria, emphasis must be given to Lichens which are amalgamation of fungi (mainly ascomycetes) and a photosynthetic partner, either cyanobacteria or green algae, or both. Cyanobacteria make association with Cycads roots and with the leaf of the water fern Azolla where cyanobacteria provide nitrogen (Rai *et al.,* 2000) and for this Azolla ferns are used as biofertilizer in many rice fields. The angiospermic partner of Cyanobacteria for symbiotic relationship is *Gunnera* where it associate with stem tissue. Cyanobacteria also form symbioses with diatoms, hornworts, liverworts, and the soil fungus *Geosiphon pyriforme* (Rai *et al.,* 2000).

Cyanobacteria played a major role even in the origin of plants. The plant chloroplast is actually a cyanobacterium living within the plant's cells. Recently, the study of complete genome sequences of cyanobacteria and *Arabidopsis thaliana* provide strong evidence of the origin of chloroplast through endosymbiosis, from a cyanobacterium (Raven and Allen, 2003).

5. Potential Commercial Uses of Cyanobacterial Toxins

Cyanobacterial toxins represent a resource of bioactive secondary metabolites which might have roles in controlling the growth of other microbes. Till date different studies in this direction have evaluated the roles of these metabolites in biomedical application beginning from employing as antibiotics against microbial infection to treatments for inhibition of cancer cells (Tan, 2007).

These compounds also bears potential to use as "natural/herbal" herbicides and insecticides. But before going to evaluate these potential uses it is necessay to evaluate their *in vitro* and *ex vitro* activities with special concern about their natural activities in natural cyanobacterial blooms. The development and use of bioactive compounds from cyanobacteria will be economically feasible only when largescale cyanobacterial culture is possible alongwith studying the ecological factors that control the production of these metabolites in natural habitat. Moreover, development of naturally occurring allelometabolies like Cyanotoxins would benefit from prior ecological assessment of these metabolites. The identification and development of cyanobacterial toxins based compounds for control of. Mosquito-borne diseases (e.g. malaria, Yellow Fever, Dengue Fever, various forms of encephalitis, West Nile Virus) possess great promises (Gubler, 1998). Cyanobacteria represent the largest part of the diet of mosquito larvae (Sangthongpitag *et al.,* 1996; Vazquez-Martinez *et al.,* 2002). Cyanobacterial toxins have already been shown to possess *Aedes aegypti* larvicidal

activities (Kiviranta, *et al.,* 1993) with very potent inhibition associated with presence of the hepatotoxic microcystins and the neurotoxic anatoxin-a. The larvicidal activities of Cyanobacterial toxin against *Culex pipiens* has already been shown by Nassar *et al.* 1999. However, much more research is needed to purify and characterize these metabolites and to determine the exact concentration of these toxins required for effective conclusion.

6. Conclusion

To conclude, the cyanobacterial bloom is the source of diverse Cyanotoxins causing threat to human, animals, crop plants and the environment in total. In addition, the use of surface water containing cyanotoxin for irrigation affect crop plants physiology as well as development and the accumulation of these toxins beyond tolerable limit cause potential health and life risk to human and animals. Thus, toxicity of cyanotoxin towards plants i.e. phytotoxicity should be of special concern and care should be taken while using the water for irrigation also and not only for drinking water alone. Also, proper initiatives should be taken towards application of these harmful toxins for beneficial uses like larvicides, herbicides and insecticides and even to fight tumor cells.

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