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Review Paper

Cyanotoxins and Their Potential Applications - A Review

B. Digamber Rao†, M. Ramesh Babu and N. Ellaswamy
Department of Botany, Kakatiya University, Warangal-506 009, A. P., India
†Corresponding Author: B. Digamber Rao

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ABSTRACT

Cyanobacteria are prokaryotic photoautotrophs capable of carrying out photosynthesis and nitrogen fixation simultaneously and they locate from different habitats are known to produce a diverse array of toxic bioactive compounds, particularly in terms of the physiology and ecology of the cyanobacteria that produce them, remains largely unknown. Although the potential of cyanobacteria as biofertiliser is well known, the attention has recently been focused on the biotechnological potential of cyanobacteria for obtaining pharmacologically active secondary metabolites which exhibit anticancer, antimicrobial, antifungal or anti-inflammatory, antiplasmodial, algicide, antiplatelet aggregation, immunosuppressive activities, expressing allelopathy character as well as the potential for development and application of these compounds as algicides, herbicides and insecticides. This review will discuss the existing evidence for the role of cyanotoxins, and specifically present relevant results from investigations into toxins of cyanobacteria from the published literature.

INTRODUCTION

Considered to be an ancient group of microorganisms with fossil records dating back 3.5 billion years ago, these prokaryotic marine cyanobacteria are ubiquitous in nature and are found in wide ranging nitches. Although they are microscopic, certain filamentous species are rather conspicuous occurring as extensive mats along tropical coastal areas. Some unicellular species can also be found living in symbiotic relationships with other marine invertebrates such as tunicates and sponges. It is well documented that certain strains e.g., *Lyngbya majuscula* and *Microcystis aeruginosa*, produced cyanotoxins that have implications in human health. These include the dermatoxin, lyngbyatoxin A, hepatotoxins, microcystins and nodularins (Carmichael 1992). The cyanobacteria such as *Fischerella ambigua*, *F. musciola*, *Nostoc commune*, *Scytonema hofmanni*, *Hapalosiphon fontinalis*, *Anabaena* sp., *Nostoc spongiae-forme*, *Microcystis aeruginosa* and *Phormidium* sp. have been reported as the main cyanobacteria to produce antimicrobial substances (Falch et al. 1995). A few studies have been done to screen cyanobacteria for production of antimicrobial substances from paddy-fields. Possibly the synthesis of highly active toxins is a defence option for cyanobacteria in these environments against other organisms like bacteria, fungi, viruses and eukaryotic microalgae (Mundt et al. 2001). In addition of these cyanotoxins, a wide range of useful secondary metabolites have also been reported and this review also highlights the allelopathic nature of certain cyanobacteria.

Certain cyanobacteria have drawn much attention as prospective and rich sources of biologically active constituents and have been identified as one of the most promising groups of organisms capable of producing bioactive compounds (Fish & Codd 1994, Schlegel et al. 1999). Cyanobacteria are known to produce metabolites with diverse biological activity such as antibacterial, antifungal, antiviral, anticancer, antiplasmodial, algicide, antiplatelet aggregation and immuno-suppressive activities (Borowitzka 1995, Jaki et al. 2000, Kajiyama et al. 1998, Patterson & Carmeli 1992, Patterson et al. 1994, Gerwick et al. 1994, Luesch et al. 2000, Papendorf et al. 1998, Papke et al. 1997, Rho et al. 1996, Koehn et al. 1992 and Ghasemi et al. 2003). The ability to produce microbial substances may be noticed not only as defensive instrument for the strains but also as a good source of new bioactive compounds from a pharmaceutical point- of-view (Soltani et al. 2005). Pandey & Pandey (2002) have studied antibacterial properties of cyanobacteria as effective and eco-friendly approach to control bacterial leaf spot disease of chilli. Recently, Sanaa (2007) have studied bioac-tive allelo-chemical compounds from *Oscillatoria* species (Egyptian isolates). A limited number of studies have suggested that some of the compounds may have ecological roles as allelochemicals, specifically including compounds that may inhibit competing sympatric macrophytes, algae and microbes. These allelochemicals may also play a role in defence against potential predators and grazers, particularly aquatic invertebrates and their larvae.

CYANOTOXINS

Cyanobacterial toxins are most well studied, and largely associated, with regard to their effects on human and environmental health. Indeed, toxicity of cyanobacterial metabolites was first reported in the scientific literature by George Francis (1878) following death of livestock in south Australia, after consumption of cyanobacteria-contaminated drinking water from Lake Alexandria. Since then, a number of incidents of human and non-human animal poisoning have been described, and several good studies on the human health effects of cyanobacterial toxins have been previously published (Chorus et al. 2000, Hitzfield et al. 2000, Duy et al. 2000, Azevedo et al. 2002, Rao et al. 2002, Wolf & Frank 2002, Griffiths & Saker 2003. Codd et al. 2005, Stewart et al. 2006 and Osborne et al. 2001).

Many secondary metabolites are potent toxins, causing health problems for animals and humans when the producer organisms occur in masses in water bodies. The toxins produced by cyanobacteria are grouped into two categories on the basis of the bioassay methods used to screen them: cytotoxins and biotoxins (Carmichael 1997). Cytotoxins are studied with cultured cell lines; there are still no data on cytotoxins from natural sources that are lethal to animals. Biotoxins are lethal to whole organisms. Considerable work, particularly by Valerie Paul and his colleagues (Paul et al. 2007, Pennings et al. 1996, Nagle & Paul 1998, Capper et al. 2006) have specifically elucidated a rather intriguing picture of the *Lyngbya majuscule*-derived toxin, lyngbyatoxin A (Fig. 1), and its role in the ecology of this species. Lyngbyatoxin A, a specific activator of protein kinase C, is most commonly associated with contact dermatitis resulting from human exposures to *L. majuscule*, however, has been shown to be toxic to fish and array of potential grazer species. It is well known fact that the widespread *Microcystis aeruginosa* is known to produce the specifically described microcystins (Fig. 2). These non-ribosomal peptides are inhibitors of serine/threonine protein phosphates 1 and 2a (PPI/2a), and most frequently are associated with hepatotoxicity in mammals and other vertebrates (Dawson 1998, Dittman & Wiegand 2006).

Schlegel et al. (1999) reported that a given organism may produce more than one bioactive substance targeted against different biochemical processes. Gromov et al. (1991), Bagchi & Marwah (1994) and Bagchi (1995) demonstrated that although the chemical structure of cyanobacteria bioactive metabolites differed, they frequently share a common mechanism of action namely inactivation of photosystem II - mediated electron flow in cyanobacteria, green algae and higher plants.

BIOACTIVE COMPOUNDS

Recent investigation on biologically active secondary metabolites from cyanobacteria led to the identification of wide range of compounds possessing antimicrobial, antiviral, antineoplastic and toxic properties (Falch et al. 1995, Moore 1996 and Namikoshi & Rinehart 1996). The ability to produce antimicrobial substances may be noticed not only as a defensive instrument for the strains but also as a good source of new bioactive compounds from pharmaceutical point-of view (Soltani et al. 2005). The cyanobacterial group is well documented for their bioactive compounds possessing antimicrobial properties, while there are only few reports available with freshwater cyanobacteria (Ghasemi et al. 2003, Sabarinathan & Ganesan 2008, Vijaya Kumar et al. 2011 and Digamber Rao et al. 2011a & b).

New antibiotics with high activity and without side effects for human and for environment are, therefore, urgently needed. Some cyanobacterial species could be a prolific resource for substances with antibacterial activity. There are numerous reports concerning the inhibiting activities from cyanobacteria against human pathogens (Kretlow et al. 1999, Abdel-Raouf 2004, Ibraheem & Abdel-Raouf 2007), fungi (Moussa & Shanab 2001, Sunil & Puranik 2007), mites (Ibraheem & Abdel-Aziz 2002, Abdel-Aziz & Abdel-Raouf 2002), algae (Issa 1999, Volk & Furkert 2006), but there is no data about effects against human pathogenic bacteria and fungi so far.

ALLELOPATHY

In addition to the role of cyanobacterial secondary metabolites as chemical defences against potential planktivores and other grazers, emerging evidence also suggests a role of these compounds in allelopathy. Allelopathy, again perhaps best described in terrestrial plant systems, in-

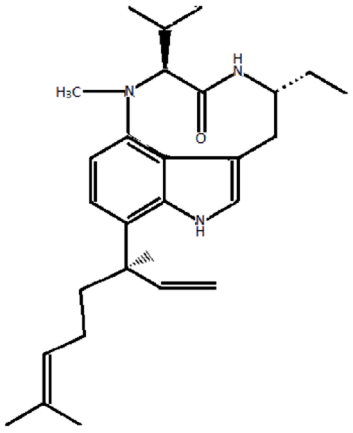

Fig. 1: Structure of lyngbyatoxin A.

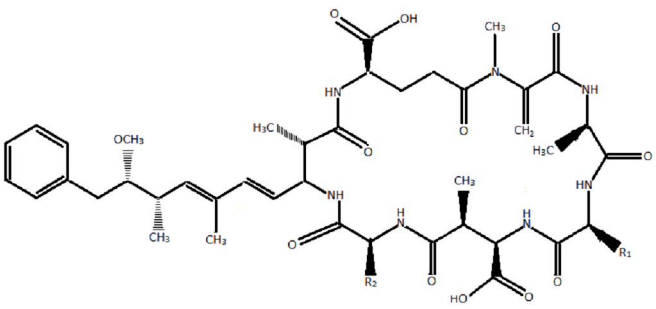

Fig. 2: Generalized structure of the microcystins: The X and Z positions are occupied by various amino acids; these positions are occupied by lysine (L;R_1=$CH_2CH(CH_3)_2$) and arginine (R; R_2 = $CH_2CH_2CH_2NHC(NH)NH_2$ in microcystin-LR, typically the most common of the more than 70 variants.

volves the use of biologically active metabolites by one species to inhibit the growth of sympatric species that might potentially compete for resources. In the case of freshwater cyanobacteria, this would mostly likely include other photoautotrophs, and particularly algae (including cyanobacteria) and even unrelated microbes, as well as possibly aquatic plants, which might compete for nutrients and light that would limit growth of cyanobacterial population. Keating (1977) demonstrated quite elegantly that extracellular components from cultures of dominant cyanobacteria isolated during succession of a single freshwater pond, specifically showed inhibitory effects on predecessor strains, but not successor strains, from this system, supporting a clear role of extracellular compounds in the succession of cyanobacterial population. Subsequent studies have continued to support the role of these allelochemicals in controlling annual variability in phytoplankton communities. Vardi et al. (2002), for example, have presented compelling evidence to suggest reciprocal non-nutritional control of population growth between microcystin-producing *Microcystis* sp. and the dinoflagellate, *Perdinium gatunense* in the mesotrophic sea of Galilee based on apparent allelo-pathic compounds, including microcystins and unknown components of the *P. gatunense* culture medium. Consequently, a growing number of studies have been identified metabolites from cyanobacteria that act as algicides (Vardi et al. 2002, Mason et al. 1982, Gromov et al. 1991). An excellent review of these studies has been previously studied by Smith & Thanh Doan (1986). Mason et al. (1982) reported the identification and characterization of a chlorinated gamma lactone, named cyanobacterin (Fig. 3) from freshwater species of *Scytonema* that specifically inhibited range of algae, including cyanobacteria and green algae, at micromolar concentrations, but had little effect on non-photosynthetic microbes. It was later found that cyanobacterin specifically inhibits photosystem II (Gleason & Case 1986). Several years later, Vepritskii et al. (1991) and Gromov et al. (1991) reported the identification of compounds from strains of *Nostoc linckia* that specifically inhibited photosynthetic algae. Named cyanobacterin LU-1 and LU-2 these compounds share no significant structural similarity to the previously characterized cyanobacterins. Both compounds, however, inhibited electron in photosystem II, and LU-1 was found to be inhibitory to cyanobacteria and other algae, but not non-photosynthetic microbes, whereas LU-2 inhibited cyanobacteria only.

Flores & Wolk (1986) and Sclegel et al. (1998) independently screened sixty-five and approximately two hundred isolates of cyanobacteria, for algicidal activity. Interestingly, it was found in these studies that anti-algal activity was largely restricted to several genera, namely *Fischerella*, *Nostoc, Anabaena, Calothrix* and *Scytonema*, primarily in sections 1V and V of the standard classification system of Rippka et al. (1979) that contain nitrogen fixing, heterocystous filamentous cyanobacteria (Flores & Wolk 1986). *Fischerella* produces the fischerellins A and B, as well as series of indole alkaloids, particularly the hapalindoles, both of which inhibit photosystem II (Srivastava et al. 1998). The latter have also been shown to inhibit RNA synthesis that has been proposed as alternative mechanism for allelopathy (Doan et al. 2001). Accordingly, the pentacyclic calothrixins, isolated from a *Calothrix* species (Rickards et al. (1999) have also been shown to inhibit RNA polymerase, as well as DNA synthesis, and proposed to be involved in allelopathic interactions (Thanh et al. 2000). In addition to cyanobacterins LU1 and LU-2, the wide spread genus, *Nostoc*, produces several others metabolites that have been associated with algicidal activity. Nostocyclamide (Todorova & Juttner 1995) is a cyclic peptide that appears to act as uncoupler of electron transport in photosynthesis. Identification of the structurally similar nostocyclomide M that also inhibits cyanobacteria. Juttner et al. (2001) suggest this molecule may belong to a family of potentially allelopathy compounds. Hirata et al. (1996) isolated and characterized a heterocyclic pigment, nostocine A, from an isolate of *Nostoc spongiaforme* that was later found (Hirata et al. 2003) to inhibit green algae and to a lesser extent, cyanobacteria. Based on the identification of inhibitory activity against cyanobacteria by Flores & Walk (1986). Becher et al. (2005) identified the carboline alkaloid, nostocarboline, which was subsequently found to inhibit various cyanobacteria, including the *Microcystis aeruginosa*, specifically by apparent effects on photosynthesis. Moreover, the inhibitory concentration against the producing strain, *Nostoc*, was considerably higher than for other cyanobacteria tested, supporting the role of the compound in allelopathy. In addition, several studies have investigated the possible allelopathic role of microcystins (Sedmark & Kosi 1998, Casanova et al. 1999,

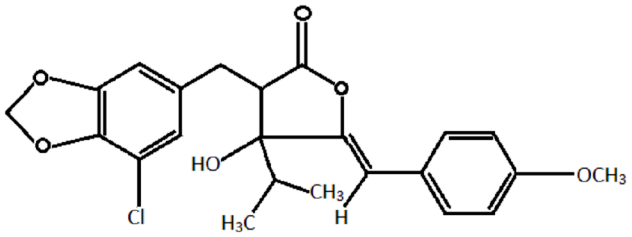

Fig. 3: Structure of cyanobacterin.

Jang et al. 2007, Microcystins have been shown to inhibit cyanobacteria, including *Nostoc, Synechococcus* and *Anabaena* species (Singh et al. 2001) and green alga, *Chlamydomonas* (Kearns & Hunter 2001). Interestingly, the presence of the green alga, *Spirogyra* as well as extracts of the alga, were found to stimulate the production of microcystins by *Oscillatoria agardhii* (Mohamed 2002) suggesting a possible production of the compound in response to potential competitors.

A number of studies on allelopathy related to microcystins have actually focused on inhibition of aquatic plants rather than microalgae (Jang et al. 2007). Pflugmacher (2002), for example, demonstrated that microcystin-LR inhibits the growth of several aquatic macrophytes, including species of *Ceratophyllum, Myriophyllum, Cladophora, Elodea* and even *Phragmites*, specifically affecting pigmentation and photosynthetic oxygen production. Jang et al. (2007) showed that microcystin-producing *Microcystis aeruginosa* negatively impacted the growth of *Lemna japonica*, and furthermore that the apparent allelopathy was reciprocal, such that exposure to the plant decreased the biomass of the cyanobacteria in culture, and concomitantly increased the production in turn of the microcystins by these cultures. Casanova et al. (1999), however, showed that though the presence of high densities of *Microcystis* cells inhibited germination and establishment of representative aquatic plants, the addition of pure microcystin alone had no effect, suggesting other possible factors. In fact, in additions to the microcystins, several other metabolites from *Microcystis* have also been shown to have inhibitory activity against photoautotrophs, specifically including kasumigamide (Ishida et al. 2000), microcin SF608 (Wiegand et al. 2002) and fatty acids (Ikawa et al. 1997). Indeed, other cases of possible allelopathy of cyanobacteria with respect to aquatic plants have also been documented. For example, in addition to inhibiting other microalgae as discussed above, nostocine A was found to inhibit root elongation by barnyard grass suggesting a possible ability to limit colonization of plants that might compete for micronutrients. This is particularly interesting as nostocine A was isolated from rice paddys. Likewise, fischerellin A, as discussed above, inhibits photosystem II in algae, has a similar activity against the *Lemna minor* with a concomitant inhibition of growth (Hagmann et al. 1996, Entzeroth et al. (128) reported that a fatty acid, 2,5-dimethyldodecanoic acid, from the marine cyanobacteria, *Lygbya majuscule*, inhibited the growth of *L. minor*. It is also worth noting that, though not our focus here, a similar number of reports have shown that metabolites from various higher plants also inhibit the growth of cyanobacteria (Nakai et al. 1999, Mulderij et al. 2006).

Though a considerable number of studies have demonstrated *in vitro* activity of cyanobacterial toxins that would suggest potential roles in allelopathy, ecological data to support this role is lacking. In fact, Babica et al. (2006) have argued that environmental concentrations of these compounds may not be high enough to support the proposed role in allelopathy. Citing microcystins as potential allelochemicals, it was noted that typical environmental concentrations of the toxin are below 10 µg/L. However, as pointed out by Hu et al. (2004), concentrations of microcystin can vary considerably and, in some cases, can exceed 100 µg/ L. Moreover, it is noteworthy that presence of both green algae and aquatic plants, including extracts from each, were shown to increase the concentration of intracellular and extracellular microcystin in exposed cyanobacteria (Mahamed 2002). Furthermore, though measured concentrations in water samples may not typically exceed 10 µg/mL, there may be localized concentration of the toxin within microenvironments, particularly including those relevant to interactions between microalgae (Hu et al. 2004, Though a good deal is known about the bioavail-ability of microcystins in freshwater systems, little is known about environmental concentrations of most other putative allelochemicals. Generally speaking, therefore, considerably more ecological research is needed to clarify the role of cyanobacterial toxins in allelopathy, as well as other proposed roles.

CONCLUSION

Over the past sixty years, a wealth of studies has clarified the importance of secondary metabolites in the ecology of organisms ranging from microorganisms to mammals. Though, currently rather limited, growing evidence continues to support a functional role of toxic or otherwise biologically active secondary metabolites from freshwater and marine cyanobacteria in the ecology of these organisms. In particular, these metabolites have seemingly complex roles in the defence against potential grazers and allelopathic interactions with competing photosynthetic algae. Still much remains to be elucidated with respect to these roles, and their implications to the evolution of aquatic systems. In addition, however, it has become equally clear that many of these same metabolites may have potential for commercial devel-

opment of, not only biomedical compounds, but also those with applications for control of algae, microbes and control of mosquito larvae and other pests particularly those that act as potential vectors of disease.

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