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Cyanobacterial and microalgal bioactive compounds – the role of secondary metabolites in allelopathic interactions

by

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Abstract

Secondary metabolites produced by plants, algae, bacteria and fungi may affect the growth and development of biological systems. This is a natural process which occurs worldwide and is known as allelopathy. A relatively small number of these allelopathic compounds has been identified. The majority of studies describe the inhibitory effect of investigated compounds, extracts, cell-free filtrates and living cells on other organisms, although stimulatory interactions have also been noticed. Allelopathic interactions in aquatic environments could provide a competitive advantage to some species over other primary producers. Furthermore, allelopathy occurs in all aquatic habitats and all groups of autotrophs are capable of producing and releasing allelopathically active compounds. Moreover, secondary metabolites obtained from phytoplankton could demonstrate other useful bioactive properties. This review is intended to summarize the current knowledge of allelopathic interactions between microalgae and cyanobacteria in aquatic environments, as well as to provide a brief overview of the ecological importance of these interactions and their potential practical application in different branches of industry.

Key words: allelopathy, bioactive compounds, secondary metabolites, microalgae, cyanobacteria

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Introduction

Organic compounds not directly involved in the normal growth, development and reproduction of living organisms are called secondary metabolites. Many of these compounds demonstrate biological activity, and potentially could affect the growth and development of biological systems. This process is observed worldwide and is known as allelopathy. This term was originally used by Molish (1937) to describe biochemical interactions between plants in terrestrial environments. In 1984, Rice defined allelopathy as any direct or indirect, negative or positive effect of chemical substances, produced and secreted by plants and microorganisms, on other plants and microorganisms. This definition was further developed by the International Allelopathy Society (IAS) in 1996. According to IAS, the term 'allelopathy' refers to any process induced by secondary metabolites produced by bacteria, fungi, algae and plants, which affects the growth and development of biological and agricultural systems. Due to their potential application in agriculture and forestry, biochemical interactions between terrestrial plants are well known. First observations were made in antiquity, for example the influence of *Juglans nigra* and *Juglans regia* on other species (Gniazdowska et al. 2004). Since then, many bioactive compounds produced by higher plants have been isolated and identified. Allelopathy, however, is not limited to terrestrial environments. Interactions caused by allelochemicals are widespread and common in freshwater, brackish and marine habitats, and occur among aquatic producers belonging to different taxonomic groups (Cembella 2003; Gross 2003). In comparison to the existing knowledge of allelopathy in terrestrial ecosystems, allelopathic interactions in aquatic habitats are still not well understood. In aquatic environments, allelochemicals may function as agents capable of incapacitating or killing the competitors. This is a chemical defense strategy and probably an important adaptive factor. Species which produce one or more bioactive compounds harmful to other species could compete better and achieve the dominance (Mulderij et al. 2005; Tillmann et al. 2008). It is known that production of bioactive secondary metabolites is highly species- or even strain-dependent (Leflaive & Ten-Hage 2007). Furthermore, allelopathic compounds released by donor species into water need to be properly hydrophilic and reach target species in effective concentrations (Gross 2003). According to the literature, allelochemicals can have several modes of action and can affect different physiological processes in living organisms, often simultaneously. Usually the influence is negative and the most common effect observed is the inhibition of target species growth. Liu et al. (2013) noticed the negative influence of *Aegiceras corniculatum*, the mangrove plant common in coastal and estuarial areas from India to Australia, on the diatom *Cyclotella caspia*. Gallic acid produced by *A. corniculatum* causes a reduction in growth and morphological changes in target species cells. Two seagrass species, *Zostera marina* and *Zostera noltii,* caused inhibition of growth of the toxic red tide dinoflagellate *Alexandrium catanella* (Laabir et al. 2013). Higher plants can also be affected by metabolites produced by microalgae or cyanobacteria. For example, living cells of *Microcystis aeruginosa* inhibited the growth of *Lemna japonica* (Jang et al. 2007), while crude extracts from *M. aeruginosa* cultures induced an oxidative stress in *Lemna gibba* (Saqrane et al. 2007). There are several reports of interactions between macrophytes and phytoplankton including cyanobacteria. Living tissues and extracts from three macrophytes, *Ulva linza*, *Corallina pilurifera* and *Sargassum thunbergii,* inhibited the growth of *Prorocentrum donghaiense* (Wang et al. 2007). Several phytoplankton species like *Heterosigma akashiwo*, *Alexandrium tamarense* and *Skeletonema costatum* were affected by the living tissue of *Ulva lactuca* (Nan et al. 2008). There are also reports on positive interactions between organisms from different taxonomic groups. Mulderij et al. (2007) observed that extract and cell-free filtrate obtained from the aquatic higher plant *Stratiotes eloides* stimulated the growth of two phytoplankton species: cyanobacteria *Synechococcus elongatus* and green algae *Scenedesmus obliquus*. One of the main reasons behind the interest in aquatic allelopathy is that bioactive secondary metabolites could be one of the key factors that promote the dominance of marine and freshwater harmful algal blooms (HABs) (Legrand et al. 2003). Moreover, phytoplankton organisms, especially dinoflagellates and cyanobacteria are considered to be a source of a wide variety of substances with bioactive potential. Allelopathic compounds isolated from cyanobacteria and other groups of phytoplankton include low-molecular-weight peptides, phenols, fatty acids, polysaccharides and alkaloids (Svircev et al. 2008). New biologically active substances could be important in many branches of industry, medicine and pharmacy. In recent years, screening for bioactive compounds produced by microorganisms

has been performed extensively all over the world.

Allelopathic interactions

In aquatic environments, chemical information is transmitted by diffusion and the main problem is the low concentration of extracellular compounds in the spaces between cells. Bioactive compounds with a low molecular weight are favored due to their faster diffusion (Leflaive & Ten-Hage 2007). Compared to allelochemicals identified in higher plants, little is known about metabolites produced by microalgae and cyanobacteria. Any such identified compounds, however, show much structural variety and include alkaloids, phenols, organic acids, long-chain fatty acids and cyclic peptides. Many allelochemicals have been described by their chemical characteristics, molecular weights and activity type, but the chemical structures of most of them remain unknown (Legrand et al. 2003). The effects of allelopathic compounds depend on the type of interaction between species, mode of action and activity. One of the commonly observed effects is inhibition of photosynthesis, usually by inhibition of electron transfer in Photosystem II (PSII). Fischerellin A produced by cyanobacteria *Fischerella musciola* is one of the identified factors affecting PSII, with up to four different targeting sites (Gross et al. 1991; Srivastava et al. 1998). Another widespread effect observed is the generation of Reactive Oxygen Species (ROS). An unidentified compound secreted by *Microcystis* sp. caused an oxidative stress in the target dinoflagellate species (Sukenik et al. 2002). There are reports on the formation of ROS in target cells by nostocine A, produced by cyanobacteria from *Nostoc* genera (Hirata et al. 2003, 2004). The generation of ROS, depending on the type and increasing concentration, may even lead to the programmed cell death or cyst formation in some species (Vardi et al. 1999; Leflaive & Ten-Hage 2007). Allelopathic interactions resulting in the cell death of target species are often observed. This is usually due to the hemolytic, lytic and membrane-disruptive properties of the secreted compounds. For example, microalgae *Prymnesium parvum* causes rapid damage to plasmatic membranes of *Rhodomonas baltica* cells. This fast process also suggests a direct impact on cell membranes instead of enzymatic processes like hydrolysis or pore formation (Schmitt et al. 1999; Skovgaard et al. 2003). Most recently, Ma et al. (2011) described the membrane-disruptive properties of compounds obtained from the dinoflagellate *Alexandrium tamarense*, but the exact mechanism of this process remains unknown. Some species, especially from cyanobacteria like *Anabaena flos-aquae,* can induce cell paralysis of target species' cells leading to faster settling, which could lead to a 'competitor-free zone' (Kearns & Hunter 2001). According to the literature data, many aquatic organisms produce extracellular enzymes, a prerequisite for nutrition and the use of complex substrates. Among cyanobacteria, several isolated strains could inhibit the activity of α-glucosidase activity (Jüttner & Wu 2000). A low-molecular-weight compound, collected from *A. flos-aquae*, inhibited the activity of α-amylase enzyme (Winder et al. 1989). Another known enzyme inhibitor is okadaic acid produced by some dinoflagellates like *Prorocentrum lima*. This compound is a serine-threonine protein phosphatase inhibitor. The stronger effect of *P. lima* exudates compared to purified acid suggests that other allelochemicals are involved (Sugg & Van Dolah 1999). Some allelochemicals can affect nucleic acid synthesis. For example, two alkaloids isolated from *Calothrix* sp. and *Fischerella* sp. (calothrixine A and hapalindole E respectively) had a negative impact on RNA polymerase activity (Doan et al. 2000). Moreover, calothrixine A can also affect DNA synthesis. Allelopathic substances may also cause morphological and ultrastructural changes. Valdor et al. (2007) reported several changes induced by living cells, extracts and pure microcystins on target organisms, including elongated and vacuolized cells, granular cell content, fragmented trichomes, an increased number of heterocysts and, in colony-forming species, a tendency to disaggregate into isolated cells. Morphological and structural modifications, including bleaching and vacuolization, thylakoid degeneration as well as disappearance of cell structures like nuclei, were observed in *Chlamydomonas* sp. cells when exposed to a crude extract obtained from *Fischerella* sp. cultures (Gantar et al. 2008). All of the described effects could lead to changes in the growth rate. Inhibition of growth induced by identified and unknown compounds is the most common allelopathic influence observed in all phytoplankton groups. For example, there are several reports on *Microcystis aeruginosa* causing the growth inhibition in other cyanobacteria as well as microalgal species (Singh et al. 2001; Sukenik et al. 2002; Żak & Kosakowska 2014). Also, cyanobacteria *Anabaena variabilis* demonstrated a negative impact on the growth of green algae *Chlorella vulgaris* (Żak et al.

2012). A similar effect induced by the dinoflagellate *Alexandrium tamarense* (Arzul et al. 1999; Wang et al. 2006) has also been observed. Although the majority of allelopathic interactions between phytoplankton species demonstrate negative character, there are reports on positive influences of one organism on another mediated by secondary metabolites. Despite the (mostly) negative impact of *Fischerella* sp. on other species, the crude extract collected from cultures of this cyanobacteria stimulated the growth of another cyanobacterium, *Nostoc* sp. (Gantar et al. 2008). The dinoflagellate *Prorocentrum minimum* increased the growth of the diatom *Skeletonema costatum* in bi-algal cultures (Tameishi et al. 2009). Exudates obtained from *Emiliania huxleyi* not only stimulated the growth of the diatom *Phaeodactylum tricornutum* but also promoted the binding and uptake of several trace metals, including Cu, Fe, Zn and Mn (Vasconcelos & Leal 2008). More information regarding allelopathic interactions among the groups of eukaryotic microalgae and prokaryotic cyanobacteria is provided in Table 1.

Ecological importance of allelopathy

According to the literature, the first observations of allelopathic interactions in aquatic environment were made in freshwater habitats and the majority of these reports concern cyanobacterial species. Little is known about the phytoplankton allelopathy in marine or, particularly, in brackish habitats. In marine environments, the majority of known interactions involve red-tide bloom-forming organisms like dinoflagellates (Cembella 2003; Gross 2003). Several ecological functions have been suggested for allelopathy. Some compounds may function as a feeding deterrent, repelling antagonistic microbes and higher order grazers. Phytoplankton species may affect microbes, zooplankton, invertebrates, fish and other vertebrates, including mammals. In particular, toxin-producing organisms with potential to form mass populations can have an impact on water resources, aquaculture, fisheries and human health (Wiegand & Pflugmacher 2004). It is known that many cyanobacterial species exhibit the optimal growth in the presence of heterotrophic bacteria. Production and excretion of extracellular metabolites may attract associated species (Kaebernick & Neilan 2001). For example, the bacterium *Pseudomonas aeruginosa* is attracted to the heterocysts of *Anabaena* sp., and these two species form a mutualistic relationship sharing the available N_2. The cyanobacterium *Microcystis aeruginosa*, demonstrates a greater cell-specific rate of CO_2 fixation in the presence of other bacteria. Furthermore, allelochemicals may also play a role in the competition between phytoplankton, compensating for competitive disadvantages like a low growth rate or low nutrient uptake. Organisms which produce and secrete bioactive compounds can also have an advantage over competitors under the same environmental conditions. Allelopathy, as a better competition strategy, could explain species succession (Wolfe 2000). The differential impact of bioactive compounds on different target species could be one of the factors causing changes in the plankton community structure (Mulderij et al. 2003). Moreover, according to Roy (2009), allelopathy acts as a strongly self-regulatory strategy of the phytoplankton community, not only as a succession regulator, but also as an effective mechanism maintaining the species diversity in the environment. The combined field observations and laboratory studies have shown that allelopathic interactions may induce bloom sequences in a eutrophic lake. Dominant cyanobacteria can inhibit other organisms, including species which were previously dominant (Keating 1977, 1978). There are other reports connecting algal succession and bloom formation with production of extracellular metabolites (Kearns & Hunter 2001; Vardi et al. 2002). For example, toxic cyanobacteria *Planktothrix agardhii* caused a rapid decrease in *Trachelomonas* (Euglenophyta) biomass during blooms in a highly eutrophic dam reservoir. Although the total number of taxa observed dropped to the minimum when the concentration of a microcystin was at the maximum, the negative impact of MC-LR on *Trachelomonas* requires further study (Grabowska & Wołowski 2014). Thus, allelopathy may play a significant role in the induction, maintenance and termination of blooms in aquatic habitats. According to the available data, allelopathic influence could increase during a stress, for example, under nutrient-deficient conditions (N or P). *Prymnesium parvum* increased the production of allelopathic compounds, negatively affecting other phytoplankton species, when the N:P ratio was altered. The addition of filtrates from cultures of *P. parvum* grown under nutrient-deficiency conditions had a stronger negative effect on target cells, compared to filtrates obtained from non-deficient cultures. This negative impact was more pronounced when target organisms were also grown under nutrient deficiency conditions (Fistarol et al. 20003; Granéli and Johansson 2003;

Table 1

Selected identified bioactive compounds produced by cyanobacteria and microalgae and their allelopathic influence on target organisms

Group/species	Compound	Target organism	Mode of action	Effect	References
Cyanobacteria					
Nostoc insulare	4,4'-dihydroxybiphenyl	cyanobacteria	unknown	growth inhibition	Volk (2005) Volk and Furket (2006)
Nostoc linckia	cyanobacterin LU-1 (phenolic compound)	phytoplankton	unknown	growth inhibition, photosynthesis inhibition, oxygen evolution	Gromov et al. 1991
Nostoc spongiaeforme	nostocine A	phytoplankton	formation of ROS	growth inhibition	Hirata et al. (2003)
Nostoc spp.	LMW bacteriocin	phytoplankton	unknown	cell death	Flores and Wolk (1986)
	nostocyclamid	phytoplankton	unknown	growth inhibition	Jüttner et al. (2001)
Scytonema hofmanni	cyanobacterin	microalgae	unknown	photosynthesis inhibition at PSII, cell death	Mason et al. (1982) Gleason and Paulson (1984) Abarzua et al. (1999)
Microalgae					
Chlorella vulgaris	chlorellin	phytoplankton	unknown	growth retardant (autoinhibition)	Pratt and Fong (1940) cited in Legrand et al. (2003)
Coolia monotis	cooliatoxin	phytoplankton	membrane damage	photosynthesis inhibition, lysis	Donner et al. (2000)
Haslea ostrearia	marennin	microalgae	unknown	growth inhibition	Pouvreau et al. (2007)
Karenia mikimotoi	gymnodimine	phytoplankton	membrane damage	lysis, cell death	Yasumoto et al. (1990) Uchida et al. (1995)
Prorocentrum lima	okadaic acid	phytoplankton	modify physiological function	growth inhibition, protein phosphatase inhibition	Sugg and Dolah (1999)
Prymnesium parvum	prymnesin	phytoplankton	membrane damage	lysis, cell death	Igarashi et al. (1998) Fistarol et al. (2003)

Fistarol et al. 2005). In addition, cell-free filtrates collected from *Chrysomchromulina* growing on the P-deficient medium, strongly inhibited the growth of the diatom *Skeletonema costatum* (Mykelstad et al. 1995). Granéli and Flynn (2006) observed the increase in *Karenia mikimotoi* toxicity under N-deficiency. Stressed conditions promote the production of allelochemicals, resulting in an advantage over potential competitors for the limited nutrient. Moreover, lysis of the co-occurring phytoplankton species releases organic N and P to the environment, which can support organisms with allelopathic potential. According to Li et al. (2012), in addition to the competition for nutrients, mixotrophy and allelopathy were the factors determining the dominant dinoflagellates species. The importance of allelopathy is probably enhanced not only in the case of abiotic stress, but also during introduction of new species into the environment. Production of an allelochemical and its continuous release, as well as delayed adaptation of target species, could give an advantage to the allelopathic species (Reigosa et al. 1999). There are suggestions that terrestrial plants and some aquatic plants use allelopathy as a spreading mechanism (Macias et al. 2008). It is possible that phytoplankton organisms may use a similar strategy during invasion of new habitats.

Bioactive properties of phytoplankton secondary metabolites and their potential practical application

Phytoplankton species from all aquatic habitats are considered to be a great source of novel secondary metabolites. In particular, dinoflagellates and cyanobacteria are known to produce a wide variety of bioactive compounds. Even a single species could produce many secondary metabolites of various chemical groups (Tan et al. 2007). Screening for new biologically active substances is performed extensively all over the world, followed by

Table 2

Bioactive properties of selected cyanobacterial compounds

Species	Compound	Activity	Target	References
Dichotrix baueriana	Bauerines A-C	antiviral	HSV-2 (Herpes Simplex Virus)	Larsen et al. (1994)
Microcystis ichtyoblabe	Ichtyopeptin A, B	antiviral	Influenza A virus	Zainuddin et al. (2007)
Nostoc ellipsosporum	Cyanovirin-N	antiviral	HIV-1 (Human Immunodeficiency Virus)	Boyd et al. (1997) Dey et al. (2000)
Scytonema varium	Scytovirin	antiviral	HIV-1	Bokesh et al. (2003)
Spirulina platensis	Calcium spirulan	antiviral	HSV-1, HIV-1, Maesles virus, Mumps virus, Influenza virus, Polio virus, Coxsackie virus	Hayashi et al. (1996)
Anabaena minutissima	Minutissamide A,D	cytotoxic (anticancer)	HT-29 (Human colon cancer cell line)	Kang et al. (2011)
Calothrix sp.	Calothrixin A	cytotoxic (anticancer)	Human T-lymphocyte cell line (Jurkat)	Chen et al. (2003)
Lyngbya majuscula	Homodolastatin 16	cytotoxic (anticancer)	Oesophageal and cervical cancer cell lines	Davies-Coleman et al. (2003)
Lyngbya sp.	Curacin A	cytotoxic (anticancer)	MCF-7 (Breast Cancer Cells)	Verdier-Pinard et al. (1998)
Microcystis aeruginosa	Aeruginoguanidine 98-A, 98C	cytotoxic (anticancer)	P388 leukemia cell line	Ishida et al. (2002)
Moorea producens	Apratoxin H, Apratoxin A sulfoxide	cytotoxic (anticancer)	NCI-H460 (Human lung cancer cells)	Thornburg et al. (2013)
Nostoc commune	Comnostin B	cytotoxic (anticancer)	KB (cervical adenocarcinoma cells) and Caco-2 (heterogeneous human epithelial colorectal adenocarcinoma cells)	Jaki et al. (2000)
Nostoc sp.	Cryptophycin 8	cytotoxic (anticancer)	TSU-prostate, LNCaP-prostate, H116-colon, MX-1 breast, cell lines	Liang et al. (2005)
Symploca sp.	Symplostatin 3	cytotoxic (anticancer)	Human Tumor Cell Lines	Luesch et al. (2002)

identification and development of phytoplankton culture techniques. Microalgal and cyanobacterial metabolites demonstrate an interesting range of biological activities, including antimicrobial and antitumoral properties (Svircev et al. 2008). Examples of bioactive properties of compounds derived from phytoplankton organisms are presented in Table 2. Allelopathic phytoplankton species in freshwater and marine environments could affect the equilibrium and limit the biodiversity of other autotrophs, invertebrates and vertebrates (Rohrlack et al. 2001; Liu et al. 2002; Pflugmacher 2002). Therefore, the use of water containing allelopathic agents including toxins for irrigation could potentially affect terrestrial plants. Allelochemicals could thus potentially be used as biodegradable, environment-friendly herbicides or biocontrol agents, as a result of their natural origin and short half lives in comparison with traditional, synthetic pesticides (Gantar et al. 2008; Qian et al. 2009). Moreover, many allelopathic compounds exert their influence through other mechanisms than commercially available herbicides and exhibit bioactivity at low concentrations, making them ideal compounds for the development of new herbicides and agrochemicals (Vyvyan 2002). In addition, some studies describe the stimulatory influence of microalgal species on seed germination (Zhongqiang et al. 2005) and there are reports on the possible use of cyanobacterial species which are capable of fixing atmospheric nitrogen as biofertilizers in agriculture (Sinha et al. 2002; Choudhury & Kennedy 2004; Obana et al. 2007; Asari et al. 2008). Furthermore, some cyanobacterial species, due to their heavy metal uptake abilities, may be used for bioremediation (Zaccaro et al. 2001). According to the literature, crude extracts obtained from toxin-producing cyanobacteria *P. agardhii* and *Dolichospermum lemmermannii* were harmful to the larvae of invertebrate *Chironomus* spp. Moreover, studies revealed that pure toxins (MC-LR and ANTX) were less toxic than extracts containing 10-times less cyanotoxins (Toporowska et al. 2014). As mentioned above, allelochemicals could affect other microorganisms and invertebrates, which could be important for controlling organisms harmful to humans. It is known that many kinds of harmful insects cause various diseases, such as mosquitoes spreading malaria, dengue and yellow fevers (Harada et al. 2000). There are several reports about the larvicidal properties of some cyanobacterial species. For example, *Oscillatoria* sp. and *Oscillatoria agardhii* have been found to be harmful to larvae of *Aedes aegypti* (Berry et al. 2008) and *Aedes albopictus* (Harada et al. 2000), respectively. According to Rao et al. (1999), the cyanobacteria *Westiellopsis* sp.

demonstrate larvicidal properties against several mosquito species, such as *Aedes aegypti*, *Anopheles stephensi*, *Culex quinquefasciatus* and *Culex tritaeniorhynchus*. Furthermore, some organisms like *Synechococcus* sp. and *Pseudoanabaena* sp. caused 100% mortality of exposed larvae (Berry et al. 2008). Secondary metabolites could be potentially used as control agents for harmful insects and protozoa. For example, malaria is a disease caused by the malaria parasite *Plasmodium falciparum*. The cyclic peptides lagunamide A and B, isolated from the marine cyanobacterium *Lyngbya majuscula*, display significant antimalarial properties (Tripathi et al. 2010). Moreover, some compounds inhibited the growth of the chloroquine-resistant strain of *P. falciparum*. These metabolites, calothrixin A and B, were isolated from the cyanobacteria *Calothrix* sp. According to the literature, cell-free filtrates, crude cell extracts and isolated identified compounds collected from phytoplankton species demonstrated antibacterial activity against Gram-positive and Gram-negative bacteria. Antifungal activity of allelochemicals has also been reported (Tuney et al. 2006; Bhagavathy et al. 2011). Microalgae from the genus *Spirogyra* show antimicrobial potential. The methanolic extract of *Spirogyra decimina* inhibited the growth of *Staphylococcus aureus* and *Proteus mirabilis*. Methanolic extracts obtained from *Spirogyra crassa* and *Spirogyra biformis* exhibited antibacterial activity against *Proteus mirabilis* and *Proteus vulgaris*, respectively. The strongest effects were observed in the case of ethanolic extracts collected from *Spirogyra grantiana*, which affected the growth of three bacterial species, namely *Escherichia coli*, *Proteus vulgaris* and *Proteus mirabilis* (Prakash et al. 2011). According to Scholtz and Liebezeit (2012), the diatom *Amphipleura pellucida* showed antibacterial activity against *Aeromonas fluvalis*. The same authors observed a negative effect of the microalgae *Leucocryptos marina* and *Hemidinium nasutum* on the growth of *Bacillus subtilis* in Agar Diffusion Assays (ADA). Moreover, they also noticed a negative effect of the microalgae *Crucigenia quadrata* on the fungi *Aspergillus niger* and *Wallemia sebi*. However, the majority of reports on bacteriostatic, bactericidal activity and negative impact on fungi is related to cyanobacteria. In 1999, Kreitlow et al. observed a negative influence of lipophilic and hydrophilic extracts of different cyanobacterial strains on the growth of several bacterial species. *Oscillatoria rubescens*, *Oscillatoria* sp. and *Limnothrix* sp. inhibited the growth of *Staphylococcus aureus*, *Bacillus subtilis* and *Micrococcus flavus*. All of these strains are Gram-positive bacteria. The obtained cyanobacterial extracts had no influence on the growth of Gram-negative bacterial strains *Escherichia coli*, *Proteus mirabilis* and *Serratia marcescens*. Antibacterial and antifungal activity of *Oscillatoria anguntissima* and *Calothrix parientina* was observed by Issa (1999). Both cyanobacterial species affected the growth of four bacterial strains, namely *Escherichia coli*, *Bacillus cereus*, *Pseudomonas aeruginosa* and *Staphylococcus aureus,* in the same way. Both cyanobacteria had a negative influence on several fungi: *Aspergillus flavus*, *Aspergillus versicolor*, *Penicillium variabile*, *Trichophyton gourgii*, *Microsporum canis* and *Chrysosporium tropicum*. A slightly stronger effect was observed in samples treated with compounds from *Calothrix parietina*. El-Sheekh et al. (2008) demonstrate that extracts from two cyanobacteria, *Anabaena wisconsinense* and *Oscillatoria curviceps,* show antibacterial and antifungal properties toward bacteria and fungi isolated from diseased fish. Both cyanobacteria affected the bacteria *Lactobacillus* sp., *Aeromonas hydrophilia*, *Bacillus firmus* and *Pseudomonas anguilliseptica,* as well as two fungi, *Aspergillus niger* and *Saprolegnia parasitica*. According to the available data, some of the isolated compounds have anti-inflammatory and antioxidant properties. Furthermore, some of the bioactive compounds isolated from microalgae and cyanobacteria may be used as antiviral agents (Tuney et al. 2006; Yasuhara-Bell & Lu 2010; Bhagavathy et al. 2011). Compounds A1 and A2 isolated from the microalgae *Cochlodinium polykrikoides*, display antiviral properties against influenza virus A and B and RSV (Respiratory Syncytial Virus) A and B. Metabolite A2 also affected the parainfluenza type 2 virus (Hasui et al. 1995). Cyanovirin-N collected from the cyanobacteria *Nostoc ellipsosporum* shows antiviral activity against SIV (Simian Immunodeficiency Virus) in monkeys and HIV-1 and HIV-2 (Human Immunodeficiency Virus) (Boyd et al. 1997). Microalgal and cyanobacterial secondary metabolites are also a promising source of antitumoral compounds. Eucapsitrione obtained from *Eucapsis* sp. and fischambiguine B produced by *Fischerella ambigua* have a cytotoxic impact on immortalized cells of the VERO line (kidney epithelial cells extracted from an African green monkey *Chlorocebus* sp.) (Mo et al. 2010; Sturdy et al. 2010). Aeruginazole A obtained from *Microcystis* sp. shows cytotoxic properties against the human leukemia cell line MOLT-4 (Raveh & Carmeli, 2010).

Very interesting results were obtained with pahayokolide A isolated from *Lyngbya* sp. This cyclic peptide demonstrates antitumoral properties toward several human cancer cell lines, including H460 (lung cancer), SKBR3 (breast cancer), HT-29 (colon cancer) and A-498 (kidney carcinoma). Most recently, Shanab et al. (2012) noticed antioxidant and anticancer activity of aqueous extracts obtained from *Nostoc muscorum* and *Oscillatoria* sp. Cytotoxic efficiency was investigated against two cell lines: EACC (Ehrlich Ascites Carcinoma Cell) and HepG2 (Human Hepatocellular cancer). Moreover, they discovered that both antioxidant and anticancer properties increased in cultures growing under nitrogen stress conditions. According to the literature, more natural products from marine phytoplankton have been found as potential lead compounds for a drug discovery. An increasing number of lipopeptides, such as hectochlorin, lyngbyabellins, lyngbyastatin or symplostatin, could be used for the development of new anticancer drugs with specific cellular targets (Tan 2007).

Summary

Microalgae and cyanobacteria produce a wide variety of secondary metabolites. Allelopathic interactions mediated by these compounds occur in all aquatic habitats and among all taxonomic groups of phytoplankton. Allelochemicals, which usually have a negative impact, may affect photosynthesis, nucleic acid synthesis, enzymatic activity and growth. They can induce morphological and ultrastructural changes or generation of ROS, and may even cause death of target cells. Some compounds may play a role in competition, especially in nutrient deficiency conditions, and may affect species succession. More importantly, allelopathy could be one of the factors responsible for maintaining the microalgal and cyanobacterial blooms. However, apart from their role in interactions between organisms and their ecological importance, such secondary metabolites often demonstrate other bioactive properties. These compounds could be potentially used as herbicides, insecticides or other biocontrol agents. Many isolated allelopathic compounds display antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral and anticancer activity. Therefore, new biologically active metabolites may play a significant role in different branches of industry, particularly in agriculture, medicine and pharmacy.

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References

Abarzua, S., Jakubowski, S., Eckert, S., Fuchs, P. (1999). Biotechnological investigation for the prevention of biofouling II. Blue-green algae as potential producers of biogenic agents for the growth inhibition of microfouling organisms. *Bot. Mar.* 42: 459-465.

Adiv, S., Ahronov-Nadborny, R., Carmeli, S. (2012). New aeruginazoles, a group of thiazole-containing cyclic peptides from Microcystis aeruginosa blooms. *Tetrahedron* 68: 1376-1383.

Arzul, G., Seguel, M., Guzman, L., Erard-Le Denn, E. (1999). Comparison of allelopathic properties in three toxic Alexandrium species. *Journal of Experimental Marine Biology and Ecology* 232: 285-295.

Asari, N., Ishihara, R., Nakajima, Y., Kimura, M., Asakawa, S. (2008). Cyanobacterial communities of rice straw left on the soil surface of a paddy field. *Biol. Fertil. Soils* 44: 605-612.

Bagchi, S.N. & Marwah J.B. (1994). Production of an algicide from cyanobacterium *Fischerella* species which inhibits photosynthetic electron transport. *Microbios* 79: 187-193.

Berry, J.P., Gantar M., Gawley, R.E., Wang M., Rein K.S. (2004). Pharmacology and toxicology of pahayokolide A, a bioactive metabolite from a freshwater species of *Lyngbya* isolated from the Florida Everglades. *Comp. Biochem. Physiol.* 139: 231-238.

Berry, J.P., Gantar, M., Perez, M.H., Berry, G., Noriega, F.G. (2008). Cyanobacterial Toxins as Allelochemicals with Potential Applications as Algaecides, Herbicides and Insecticides. *Marine Drugs* 6: 117-146.

Bhagavathy, S., Sumathi, P., Jancy Sherene Bell, I. (2011). Green algae Chlorococcum humicola-a new source of bioactive compounds with antimicrobial activity. Asian Pacific *Journal of Tropical Biomedicine* S1-S7.

Bokesch, H.R., O'Keefe, B.R., McKee, T.C., Pannell, L.K., Patterson, G.M.L. et al. (2003). A potent novel anti-HIV protein from the cultured cyanobacterium *Scytonema varium*. *Biochemistry* 42: 2578-2584.

Bonazzi, S., Barbaras, D., Patiny, L., Scopelliti, R., Schneider, P. et al. (2010). Antimalarial and antitubercular nostocarboline and eudistomin derivatives: Synthesis, in vitro and in vivo

biological evaluation. *Bioorg. Med. Chem*. 18: 1464-1476.

Boyd, M.R., Gustafson, K.R., McMahon, J.B., Shoemaker, R.H., O'Keefe, B.R. et al. (1997). Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: potential applications to microbicide development. *Antimicrob Agents Chemother*. 41(7): 1521-30.

Boyd, M.R. (1999). Papuamides A-D, HIV-inhibitory and cytotoxic depsipeptides form the sponges Theonella mirabilis and Theonella swinhoei collected in Papua New Guinea. *J. Am. Chem. Soc*. 121: 5899-5909.

Cembella, A. (2003). Chemical ecology of eukaryotic microalgae in marine ecosystems. *Phycologia*. 42: 420-447.

Chen, X., Smith, G.D., Waring, P. (2003). Human cancer cell (Jurkat) killing by the cyanobacterial metabolite calothrixin A. *J. Appl. Phycol*. 15: 269-277.

Choudhury, A.T.M.A., Kennedy, I.R. (2004). Prospects and potentials for systems of biological nitrogen fixation in sustainable rice production. *Biol. Fertil. Soils*. 39: 219-227.

Davies-Coleman, M., Dzeha, T.M., Gray, C.A., Hess, S., Pannell, L.K., Hendricks, D.T. (2003). Isolation of homodolastatin 16, a new cyclic depsipeptide from a Kenyan collection of Lyngbya majuscula. *J. Nat. Prod.* 66: 712-715.

Dey, B., Lerner, D.L., Lusso, P., Boyd, M.R., Elder, J.H. et al. (2000). Multiple antiviral activities of cyanovirin-N: blocking of human immunodeficiency virus type 1 gp120 interaction with CD4 and coreceptor and inhibition of diverse enveloped viruses. *J. Virol.* 74: 4562-4569.

Doan, N.T., Rickards, R., Rothschild, J., Smith, G.D. (2000). Allelopathic actions of the alkaloid 12-epi-hapalindole E isonitrile and calothrixin A from cyanobacteria of the genera *Fischerella* and *Calothrix*. *J. Appl. Phycol*. 12: 409-416.

Donner, G., Platt-Rouloff, L., Brümmer, E., Elbrächter, M. (2000). A calcium dependent allelopathic effect of the dinoflagellate Coolia monotis on the chlorophyceae Dunaliella salina. In: Abstracts, 9th International Conference on Harmful Algal Blooms, 7-11 February, Hobart, Tasmania, Australia, p. 112.

El-Sheekh, M. M., Dawah A. M., Abd El-Rahman A. M., El-Adel H. M., Abd El-Hay R. A. (2008). Antimicrobial activity of the cyanobacteria *Anabaena wisconsinense* and *Oscillatoria curviceps* against pathogens of fish in aquaculture. *Annals of Microbiology* 58(3): 527-534.

Fistarol, G.O., Legrand, C., Granéli, E. (2003). Allelopathic effect of *Prymnesium parvum* on a natural plankton community. *Mar. Ecol. Prog. Ser*. 255: 115-125.

Fistarol, G.O., Legrand, C., Granéli, E. (2005). Allelopathic effect on a nutrient-limited phytoplankton species. *Aquat. Microb. Ecol*. 41: 153,161.

Flores, E. and Wolk, C.P. (1986). Production, by filamentous, nitrogen-fixing cyanobacteria, of a bacteriocin and of other antibiotics that kill related strains. *Arch. Microbiol*. 145: 215-219.

Gantar, M., Berry, J.P., Thomas, S., Wang, M., Perez, R. et al. (2008). Allelopathic activity among *Cyanobacteria* and microalgae isolated from Florida freshwater habitats. FEMS *Microbiol. Ecol*. 64(1): 55-64.

Gleason, F.K. and Paulson, J.L. (1984). Site of action of the natural algicide, cyanobacterin, in the bluegreen alga, *Synechococcus* sp. *Arch. Microbiol*. 138: 273-277.

Gniazdowska, A., Oracz, K., Bogatek, R. (2004). Allelopathy – new interpretations of plant – plant interactions. (In Polish, English summary). *Kosmos* 53(2): 207-217.

Grabowska, M. & Wołowski, K. (2014). Development of *Trachelomonas* species (Euglenophyta) during blooming of *Planktothrix agardhii* (Cyanoprokaryota). *Ann. Limnol. – Int. J. Lim*. 50: 49-57. DOI: 10.1051/limn/2013070.

Granéli, E., Johansson, N. (2003). Increase in the production of allelopathic substances by *Prymnesium parvum* cells grown under N- or P-deficient conditions. *Harmful Algae* 2: 135-145.

Granéli, E., Flynn, K. (2006). Chemical and physical factors influencing toxin content. In: E. Granéli & T.J. Turner (Eds.) *Ecology of Harmful Algae*. Ecological Studies Series 189, Springer-Verlag, Berlin and Heidelberg, pp. 229-241.

Gromov, B.V., Verpitskiy, A.A., Titova, N.N., Mamkayeva, K.A., Aleksandrova ,O.V. (1991). Production of the antibiotic cyanobacterin LU-1 by *Nostoc linckia* CALU 892 (cyanobacterium). *J. Appl. Phycol*. 3: 55-60.

Gross, E.M., Wolk, C.P., Jüttner, F. (1991). Fischerellin, a new allelochemical from the freshwater cyanobacterium *Fischerella musciola*. *Journal of Phycology* 27: 686-692.

Gross, E.M. (2003). Allelopathy of aquatic autotrophs. *Plant Science* 22: 313-339.

Harada, K.-I., Suomalainen, M., Uchida, H., Masul, H., Ohmura, K. et al. (2000). Insecticidal compounds against mosquito larvae from *Oscillatoria agardhii* strain 27. *Environ Toxicol.* 15: 114-9.

Hasui, M., Matsuda, M., Okutani, K., Shigeta, S. (1995). In vitro antiviral activities of sulfated polysaccharides from a marine microalga (*Cochlodinium polykrikoides*) against human immunodeficiency virus and other enveloped viruses. *Int. J. Biol. Macromol*. 17: 293-297.

Hayashi, K., Hayashi, T., Kojima, I.A. (1996). Natural sulfated polysaccharide, calcium spirulan, isolated from Spirulina platensis: in vitro and ex vivo evaluation of anti-herpes simplex virus and anti-human immunodeficiency virus activities. AIDS *Res. Hum. Retrovir.* 12: 1463-71.

Hirata, K., Yoshitomi, S., Dwi, S., Iwabe, O., Mahakhant, A. et al.

(2003). Bioactivities of Nostocine A produced by a freshwater cyanobacterium *Nostoc spongiaeforme* TISTR 8169. *Journal of Bioscience and Bioengineering* 95(5): 512-517.

Hirata, K., Yoshitomi, S., Dwi, S., Iwabe, O., Mahakant, A. et al. (2004). Generation of reactive oxygen species undergoing redox cycle of nostocine A: a cytotoxic violet pigment produced by freshwater cyanobacterium *Nostoc spongiaeforme*. *Journal of Biotechnology* 110: 29-35.

Hu, Z., Liu, Y., Li, D., Dauta, A. (2005). Growth and antioxidant system of the cyanobacterium *Synechococcus elongatus* in response to microcystin-RR. *Hydrobiologia* 534: 23-29.

Igarashi, T., Aritake, S., Yasumoto, T. (1998). Biological activities of prymnesin-2 isolated from a red tide alga *Prymnesium parvum*. *Natural Toxins* 6: 35-41.

International Allelopathy Society (1996). First world congress on allelopathy. A science for the future.

Ishida, K. & Murakami, M. (2000). Kasumigamide, an antialgal peptide from the cyanobacterium *Microcystis aeruginosa*. *J. Org. Chem*. 65: 5898-5900.

Ishida, K., Matsuda, H., Okita, Y., Murakami, M. (2002). Aeruginoguanidines 98-A–98-C: cytotoxic unusual peptides from the cyanobacterium *Microcystis aeruginosa*. *Tetrahedron* 58: 7645-7652.

Issa A.A. (1999). Antibiotic production by the cyanobacteria *Oscillatoria angustissima* and *Calothrix parietina*. *Environmental Toxicology and Pharmacology* 8: 33-37.

Jaki, B., Orjala, J., Heilmann, J., Linden, A., Vogler, B. et al. (2000). Novel extracellular diterpenoids with biological activity from the cyanobacterium *Nostoc commune*. *J. Nat. Prod.* 63: 339-343.

Jang, M.-H., Ha, K., Takamura, N. (2007). Reciprocal allelopathic responses between toxic cyanobacteria (Microcystis aeruginosa) and duckweed (Lemna japonica). *Toxicon.* 49: 727-733.

Jüttner, F. & Wu, J.-T. (2000). Evidence of allelochemical activity in subtropical cyanobacterial biofilms of Taiwan. *Arch. Hydrobiol.* 147: 505-517.

Jüttner, F., Todorova, A.K., Walch, N., von Philipsborn, W. (2001). Nostocyclamide M: a cyanobacterial cyclic peptide with allelopathic activity from *Nostoc* 31. *Phytochemistry* 57: 613-619.

Kaebernick, M. & Neilan, B.A. (2001) Ecological and molecular investigations of cyanotoxin production. – FEMS *Microbiol. Ecol*. 35: 1-9.

Kang, H., Krunic, A., Shen, Q., Swanson, S.M., Orjala, J. (2011). Minutissamides A-D, antiproliferative cyclic decapeptides from the cultured cyanobacterium Anabaena minutissima. *J. Nat. Prod*. 74: 1597-1605.

Kaya, K., Mahakhant, A., Keovara, L., Sano, T., Kubo, T. et al. (2002). Spiroidesin, a novel lipopeptide from the cyanobacterium *Anabaena spiroides* that inhibits cell growth of the cyanobacterium *Microcystis aeruginosa*. *J. Nat. Prod.* 65: 920-921.

Kearns, K.D. & Hunter M.D. (2001). Toxinproducing *Anabaena flos-aquae* induces settling of *Chlamydomonas reinhardtii*, a competing motile alga. *Microb. Ecol*. 42: 80-86.

Keating, K.I. (1977). Allelopathic influence on bluegreen bloom sequence in a eutrophic lake. *Science* 196: 885-887.

Keating, K.I. (1978). Blue-green algal inhibition of diatom growth: transition from mesotrophic to eutrophic community structure. *Science* 199: 971-973.

Kreitlow, S., Mundt, S., Lindequist, U. (1999). Cyanobacteria – a potential source of new biologically active substances. *Journal of Biotechnology* 70: 61-63.

Laabir, M., Grignon-Dubois, M., Masseret, E., Rezzonico, B., Soteras, G. et al. (2013). Algicidal effects of *Zostera marina* L. and *Zostera noltii* Hornem. Extracts on the neuro-toxic bloom-forning dinoflagellate *Alexandrium catenella*. *Aquatic Botany* 111: 16-25.

Larsen, L.K., Moore, R.E., Patterson, G.M.L. (1994). b-Carbolines from the bluegreen alga Dichothrix baueriana. *J. Nat. Prod.* 57: 419-421.

Leflaive, J. & Ten-Hage, L. (2007). Algal and cyanobacterial secondary metabolites in freshwaters: a comparison of allelopathic compounds and toxins. *Freshwater Biology* 52: 199-214.

Legrand, C., Reigefors, K., Fistarol, G.O., Graneli, E. (2003). Allelopathy in phytoplankton – biochemical, ecological and evolutionary aspects. *Phycologia* 42: 406-419.

Li, J., Glibert, P.M., Alexander, J.A., Molina, M.E. (2012). Growth and competition of several harmful dinoflagellates under different nutrient and light conditions. *Harmful Algae* 13: 112-125.

Liang, J., Moore, R.E., Moher, E.D., Munroe, J.E., Al-awar, R.S. et al. (2005). Cryptophycins-309, 249 and other cryptophycin analogs: Preclinical efficacy studies with mouse and human tumors. *Investigational New Drugs* 23: 213-224.

Linington, R.G., González, J., Ureña, L.-D., Romero, L.I., Ortega-Barría, E. et al. (2007). Venturamides A and B: antimalarial constituents of the Panamanian marine cyanobacterium *Oscillatoria* sp. *J. Nat. Prod*. 70: 397-401.

Linington, R.G., Clark, B.R., Trimble, E.E., Almanza, A., Ureña, L.-D. et al. (2009). Antimalarial Peptides from Marine Cyanobacteria: Isolation and Structural Elucidation of Gallinamide A. *J. Nat. Prod.* 72(1): 14-17. DOI: 10.1021/np8003529.

Liu, Y., Song, L., Li, X., Liu, T. (2002). The toxic effects of microcystin-LR on embryo– larval and juvenile development

of loach, *Misguruns mizolepis* Gunthe. *Toxicon* 40: 395-399.

Liu, Y., Li, F., Huang, Q. (2013). Allelopathic effects of gallic acid from *Aegiceras corniculatum* on *Cyclotella caspia*. *Journal of Environmental Sciences* 25(4): 776-784.

Luesch, H., Yoshida, W.Y., Moore, R.E., Paul, V.J., Mooberry, S.L. et al. (2002). Symplostatin 3, a new dolastatin 10 analogue from the marine cyanobacterium Symploca sp. VP452. *J. Nat. Prod.* 65: 16-20.

Ma, H., Krock, B., Tillmann, U., Bickmeyer, U., Graeve, M. et al. (2011). Mode of action of membrane-disruptive lytic compoundsfrom the marine dinoflagellate *Alexandrium tamarense*. *Toxicon* 58: 247-258.

Macías, F.A., Galindo, J.L.G., García-Díaz, M.D., Galindo, J.C.G. (2008). Allelopathic agents from aquatic ecosystems: potential biopesticides models. *Phytochem. Rev*. 7: 155-178.

Mason, C.P., Edwards, K. R., Carlson, R. E., Pignatello, J., Gleason, F.K. et al. (1982). Isolation of chlorine-containing antibiotic from the freshwater cyanobacterium *Scytonema hofmanni*. *Science* 215: 400-402.

McPhail, K.L., Correa, J., Linington, R.G., González, J., Ortega-Barría, E. et al. (2007). Antimalarial linear lipopeptides from a Panamanian strain of the marine cyanobacterium Lyngbya majuscule. *J. Nat. Prod.* 70: 984-988.

Mo, S., Krunic, A., Pegan, S.D., Franzblau, S.G., Orjala, J. (2009). An antimicrobial guanidine-bearing sesterterpene from the cultured cyanobacterium *Scytonema* sp. *J. Nat. Prod.* 72: 2043-2045.

Mo, S., Krunic, A., Santarsiero, B.D., Franzblau, S.G., Orjala, J. (2010). Hapalindolerelated alkaloids from the cultured cyanobacterium *Fischerella ambigua*. *Phytochemistry* 1: 2116-2123.

Mohamed, Z.A. (2013). Toxic effect of norharmane on a freshwater plankton community. *Ecohydrology & Hydrobiology* 13: 226-232.

Molish, H. (1937). Der Einfluss einer Pflanze auf die andere: Allelopathie. Fisher Verlag, Jena 106 pp. (In German).

Moon, S., Chen, J.L., Moore, R.E., Patterson, G.M.L. (1992). Calophycin, a fungicidal cyclic decapeptide from the terrestrial blue-green alga *Calothrix fusca*. *J. Org. Chem*. 57: 1097-1103.

Moore, R.E., Cheuk, C., Patterson, G.M.L. (1984). Hapalindoles: new alkaloids from the blue-green alga *Hapalosiphon fontinalis*. *J. Am. Chem. Soc*. 106: 6456-6457.

Mulderij, G., van Donk, E., Roelofs, G.M. (2003). Differential sensitivity of green algae to allelopathic substances from *Chara*. *Hydrobiologia* 491: 261-271.

Mulderij, G., Mooij, W.M., Smolders, A.J.P., van Donk, E. (2005). Allelopathic inhibition of phytoplankton by exudates from Stratiotes aloides. *Aquatic Botany* 82: 284-296.

Mulderij, G., Mau, B., van Donk, E., Gross, E.M. (2007). Allelopathic activity of *Stratiotes aloides* on phytoplankton – towards identification of allelopathic substances. *Hydrobiologia* 584: 89-100.

Myklestad, S.M., Ramlo, B., Hestmann, S. (1995). Demonstration of strong interaction between the flagellate *Chrysochromulina polylepis* (Prymnesiophyceae) and a marine diatom. In: P. Lassus, G. Arzul, E. Erard-Le Denn et al. (Eds), *Harmful Marine Algal Blooms* (pp. 633-638). Lavoisier, Intercept Ltd.

Nan, C., Zhang, H., Lin, S., Zhao, G., Liu, X. (2008). Allelopathic effects of *Ulva lactuca* on selected species of harmful bloom-forming microalgae in laboratory cultures. *Aquatic Botany* 89: 9-15.

Neuhof, T., Schmieder, P., Preussel, K., Dieckmann, R., Pham, H. et al. (2005). Hassallidin A, a glycosylated lipopeptide with antifungal activity from the cyanobacterium *Hassallia* sp. *J. Nat. Prod*. 68: 695-700.

Obana, S., Miyamoto, K., Morita, S., Ohmori, M. et al. (2007). Effect of *Nostoc* sp. On soil characteristics, plant growth and nutrient up take. *J. Appl. Phycol.* 19: 641-646.

Qian, H., Xu, X., Chen, W., Jiang, H., Jin, Y. et al. (2009). Allelochemical stress causes oxidative damage and inhibition of photosynthesis in *Chlorella vulgaris*. *Chemosphere* 75(3): 368-75. DOI:10.1016/j.chemosphere.2008.12.040.

Pflugmacher, S. (2002). Possible allelopathic effects of cyanotoxins, with reference to microcystin-LR, in aquatic ecosystems. *Environ. Toxicol*. 17(4): 407-413.

Pouvreau, J.-B., Housson, E., Le Tallec, L., Morançais, M., Rincé, Y. et al. (2007). Growth inhibition of several marine diatom species induced by the shading effect and allelopathic activity of marennine, a blue-green polyphenolic pigment of the diatom *Haslea ostrearia* (Gaillon/Bory) Simonsen. *Journal of Experimental Marine Biology and Ecology* 352: 212-225.

Prakash, J.W., Antonisamy, J.M., Jeeva, S. (2011). Antimicrobial activity of certain fresh water microalgae from Thamirabarani River, Tamil Nadu, South India. *Asian Pacific Journal of Tropical Biomedicine* 1 (Suppl. 2): S170-S173.

Pratt, D.M., Fong, J. (1940). Studies on *Chlorella vulgaris*. II. Further evidence that *Chlorella* cells form a growth-inhibiting substance. *American Journal of Botany* 27: 431-436.

Rao, D.R., Thangavel, C., Kabilan, L., Suguna, S., Mani, T.R., Shanmugasundaram S. (1999). Larvicidal properties of the cyanobacterium *Westiellopsis* sp. against mosquito vectors. *Trans. Royal Soc. Trop. Med. Hyg.* 93: 232.

Raveh, A. & Carmeli, S. (2007). Antimicrobial ambiguines from the cyanobacterium *Fischerella* sp. collected in Israel. *J. Nat. Prod*. 70: 196-201.

Raveh, A. & Carmeli, S. (2010). Aeruginazole A, a novel

thiazole-containing cyclopeptide from the cyanobacterium *Microcystis* sp. *Org. Lett.* 12: 3536-3539.

Reigosa, M.J., Sánchez-Moreiras, A., González, L. (1999). Ecophysiological approach in allelopathy. *Crit. Rev. Plant Sci*. 18: 577-608.

Rice, E.L. (1984). Allelopathy, 2nd ed. Academic Press, Orlando, FL, 423 p.

Rohrlack, T., Henning, M., & Kohl, J.G. (2001). Isolation and characterization of colonyforming *Microcystis aeruginosa* strains. In: I. Chorus (Ed.), *Cyanotoxins – Occurrence, Causes, Consequences* (pp. 152-158). Springer-Verlag, Berlin.

Roy, S. (2009). Do phytoplankton communities evolve through a self-regulatory abundance–diversity relationship? *BioSystems* 95: 160-165.

Rzymski, P., Poniedziałek, B., Kokociński, M., Jurczak, T., Lipski, D. et al. (2014). Interspecific allelopathy in cyanobacteria: Cylindrospermopsin and *Cylindrospermopsis raciborskii* effect on the growth and metabolism of *Microcystis aeruginosa*. *Harmful Algae* 35: 1-8.

Saqrane, S., El Ghazali, I., Ouahid, Y., El Hassni, M., El Hadrami, I. et al. (2007). Phytotoxic effects of cyanobacteria extract on the aquatic plant *Lemna gibba*: Microcystin accumulation, detoxication and oxidative stress induction. *Aquatic Toxicology* 83: 284-294.

Schmitt, T.M., Hay, M.E., O'Brien, A.D. (1999). Bacterial toxins: friends or foes? *Emerging Infectious Diseases* 5(2): 1-6.

Scholz, B. & Liebezeit, G. (2012). Screening for biological activities and toxicological effects of 63 phytoplankton species isolated from freshwater, marine and brackish water habitats. *Harmful Algae* 20: 58-70.

Shanab, S.M.M., Mostafa, S.S.M., Shalaby, E.A., Mahmoud, G.I. (2012). Aqueous extracts of microalgae exhibit antioxidant and anticancer activities. *Asian Pacific Journal of Tropical Biomedicine* 608-615.

Singh, D.P., Tyagi, M.B., Kumar, A., Thakur, J.K., Kumar, A., (2001). Antialgal activity of a hepatotoxin-producing cyanobacterium, Microcystis aeruginosa. *World Journal of Microbiology & Biotechnology* 17: 15-22.

Sinha, S.K., Verma, D.C., Dwivedi, C.P. (2002). Role of green manure (Sesbania rostrata) and biofertilizers (Blue-green algae and Azotobacter) in rice-wheat cropping system in state of Uttar Pradesh, India. *Physiol. Mol. Biol. Plants* 8: 105-110.

Skovgaard, A., Legrand, C., Hansen, P.J., Granéli, E. (2003). Effects of nutrient limitation on food uptake in the toxic haptophyte *Prymnesium parvum*. *Aquat. Microb. Ecol.* 31: 259-265.

Srivastava, A., Juttner, F., Strasser, R.J. (1998). Action of the allelochemical fischerellin A on photosystem. *Biochimica et Biophusica Acta* 1364: 326-336.

Sturdy, M., Krunic, A., Cho, S., Franzblau, S., Orjala, J. (2010). Eucapsitrione, an anti-*Mycobacterium tuberculosis* anthraquinone derivative from the cultured freshwater cyanobacterium *Eucapsis* sp. *J. Nat. Prod.* 73: 1441-1443.

Sugg, L.M. & van Dolah F.M. (1999). No evidence for an allelopathic role of okadaic acid among ciguateraassociated dinoflagellates, *J. Phycol.* 35: 93-103.

Sukenik, A., Eskhol, R., Livne, A., Hadas, O., Rom, M. et al. (2002). Inhibition of growth and photosynthesis of the dinoflagellate *Peridinium gatunense* by *Microcystis* sp. (cyanobacteria): A novel Allelopathic mechanism. *Limnology and Oceanography* 47(6): 1656-1663.

Svircev, Z., Cetojevic-Simin, D., Simeunovic, J., Karaman, M. & Stojanovic, D. (2008). Antibacterial, antifungal and cytotoxic activity of terrestrial cyanobacterial strains from Serbia. *Sci. China Ser. C-Life Sci.* 51(10): 941-947.

Tameishi, M., Yamasaki, Y., Nagasoe, S., Shimasaki, Y., Oshima, Y. et al. (2009). Allelopathic effects of the dinophyte *Prorocentrum minimum* on the growth of the bacillariophyte *Skeletonema costatum*. *Harmful Algae* 8: 421-429.

Tan, L.T. (2007). Bioactive natural products from marine cyanobacteria for drug discovery. *Phytochemistry* 68: 954-979.

Thornburg, C.C., Cowley, E.S., Sikorska, J. (2013). Apratoxin H and apratoxin A sulfoxide from the Red Sea cyanobacterium Moorea producens. *J. Nat. Prod.* 76: 1781-1788.

Tillmann, U., Alpermann ,T., John, U., Cembella, A. (2008). Allelochemical interactions and short-term effects of the dinoflagellate Alexandrium on selected photoautotrophic and heterotrophic protists. *Harmful Algae* 7: 52-64.

Toporowska, M., Pawlik-Skowrońska, B., Kalinowska, R. (2014). Accumulation and effects of cyanobacterial microcystins and anatoxin-a on benthic larvae of *Chironomus* spp. (Diptera: Chironomidae). *Eur. J. Entomol.* 111(1): 83-90. DOI: 10.14411/eje.2014.010.

Tripathi, A., Puddick, J., Prinsep, M.R., Rottmann, M., Tan, L.T. (2010). Lagunamides A and B: cytotoxic and antimalarial cyclodepsipeptides from the marine cyanobacterium Lyngbya majuscula. *J. Nat. Prod.* 29;73(11): 1810-4. DOI: 10.1021/np100442x.

Tüney, U., Çadirci, H.B., Ünal, D., Sukatar, A. (2006). Antimicrobial Activities of the Extracts of Marine Algae from the Coast of Urla (Üzmir, Turkey) *Turk. J. Biol.* 30: 171-175.

Uchida, T., Yamaguchi, M., Matsuyama, Y., Honjo, T. (1995). The red tide dinoflagellate *Heterocapsa* sp. kills *Gyrodinium instriatum* by cell contact. *Mar. Ecol. Prog. Ser.* 118: 301-303.

Valdor, R., Aboal, M. (2007). Effects of living cyanobacteria,

cyanobacterial extracts and pure microcystins on growth and ultrastructure of microalgae and bacteria. *Toxicon* 49: 769-779.

Vardi, A., Berman-Frank, I., Rozenberg, T., Hadas, O., Kaplan, A. et al. (1999). Programmed cell death of the dinoflagellate *Peridinium gatunense* is mediated by CO_2 limitation and oxidative stress. *Curr. Biol.* 9: 1061-1064.

Vardi, A., Schatz, D., Beeri, K., Motro, U., Sukenik, A. et al. (2002). Dinoflagellate-cyanobacterium communication may determine the composition of phytoplankton assemblage in a mesotrophic lake. *Curr. Biol.* 12: 1767-1772.

Vasconcelos, M.T.S.D., Leal, M.F.C. (2008). Exudates of different marine algae promote growth and mediate trace metal binding in Phaeodactylum tricornutum. *Marine Environmental Research* 66: 499-507.

Verdier-Pinard, P., Lai, J.-Y., Yoo, H.-D., Yu, J., Marquez, B. et al. (1998). Structure-Activity Analysis of the Interaction of Curacin A, the Potent Colchicine Site Antimitotic Agent, with Tubulin and Effects of Analogs on the Growth of MCF-7 Breast Cancer Cells. *Mol. Pharmacol.* 53(1): 62-76.

Volk, R.-B. (2005). Screening of microalgal culture media for the presence of algicidal compounds and isolation of two bioactive metabolites, excreted by the cyanobacteria *Nostoc insulare* and *Nodularia harveyana*. *J. Appl. Phycol.* 17: 339-347.

Volk, R.-B. & Furkert, F.H. (2006). Antialgal, antibacterial and antifungal activity of two metabolites produced and excreted by cyanobacteria during growth. *Microbiol. Res.* 161: 180-186.

Vyvyan, J.R. (2002). Allelochemicals as leads for new herbicides and agrochemicals. *Tetrahedron* 58: 1631-1646.

Wang, Y., Yu, Z., Song, X., Zhang, S. (2006). Interactions between the bloom-forming dinoflagellates Prorocentrum donghaiense and Alexandrium tamarense in laboratory cultures. *Journal of Sea Research* 56: 17-26.

Wang, R., Xiao, H., Wang, Y., Zhou, W., Tang, X. (2007). Effects of three macroalgae, *Ulva linza* (Chlorophyta), *Corallina pilulifera* (Rhodophyta) and *Sargassum thunbergii* (Phaeophyta) on the growth of the red tide microalga *Prorocentrum donghaiense* under laboratory conditions. *Journal of Sea Research* 58: 189-197.

Wiegand, C., Pflugmacher, S. (2004). Ecotoxicological effects of selected cyanobacterial secondary metabolites a short review. *Toxicology and Applied Pharmacology* 203: 201- 218.

Winder, J.S., Canneli, R.J.P., Walker, J.M., Delbarre, S., Francisco, C. et al. (1989). Glycosidase inhibitors from algae. *Biochem. Soc. T.* 17: 1030-1031.

Wolfe, G.V. (2000). The chemical defence ecology of marine unicellular plankton: constraints, mechanisms and impacts. *Biological Bulletin* 198: 225-244.

Yasuhara-Bell, J. & Lu, Y. (2010). Marine compounds and their antiviral activities. *Antiviral Research* 86: 231-240.

Yasumoto, T., Underdal, B., Aune, T., Hormazabal, V., Skulberg, O.M. et al. (1990). Screening for haemolytic and ichthyotoxic components of Chrysochromulina polylepis and Gyrodinium aureolum from Norewegian coastal waters. In E. Granéli, B. Sunderström, L. Edler, D.M. Anderson (Eds.), *Toxic marine phytoplankton* (pp. 436-440).

Zaccaro, M.C., Salazar, C., De Caire, G.Z., De Cano, M.S., Stella, A.M. (2001). Lead toxicity in cyanobacterial porphyrin metabolism. *Environ Toxicol Water Qual* 16: 61-67.

Zainuddin, E.N., Mentel, R., Wray, V., Jansen, R., Nimtz, M. et al. (2007). Cyclic depsipeptides, ichthyopeptins A and B, from *Microcystis ichthyoblabe*. *J. Nat. Prod.* 70: 1084-1088.

Zhongqiang, L., Yu, D., Manghui, T. (2005). Seed germination of three species of *Vallisneria* (Hydrocharitaceae) and the effects of freshwater microalgae. *Hydrobiologia* 544: 11-18.

Żak, A., Musiewicz, K., Kosakowska, A. (2012). Allelopathic activity of the Baltic cyanobacteria against microalgae. *Estuarine, Coastal and Shelf Science* 112: 4-10. DOI: doi:10.1016/j.ecss.2011.10.007.

Żak, A. & Kosakowska A. (2014). Allelopathic Influence of Cyanobacteria *Microcystis aeruginosa* on Green Algae *Chlorella vulgaris*. *Insights on Environmental Changes, GeoPlanet: Earth and Planetary Sciences* 141-150. DOI: 10.1007/978-3-319-03683-0_10.