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REVIEW

Biomedical potential of cyanobacteria and algae

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ABSTRACT Cyanobacteria have appeared on the primordial Earth over three billion years ago and still thrive in most habitats. These photosynthetic microbes have remarkable genetic plasticity and variability and have evolved an amazing arsenal of biochemical pathways that exert defence mechanisms and produce metabolites unique to them. By forming plastids, endosymbiont cyanobacteria contributed to the development of plants. Algae, the simplest plants, thrive in similar habitats and face the same challenges of the ever changing environment as cyanobacteria; and they have maintained similarity to them, with respect to production of unique metabolites and utilizing unique pathways. The exploration of these natural compounds and the biochemical pathways leading to their production provide excellent tools in fighting some major challenge that mankind needs to face in our days. In this contribution we briefly list the benefits that the genetics of these microbes and the produced compounds can offer, with emphasis on possible medical relevance. We mention applications in basic science, industry and agriculture, and list the potentials in medical drug development, therapy and nutrition of some enzymes, polysaccharides, polyphenols, pigments, peptides and lipids, among others, in the current state of the world-wide research on the topic.
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KEY WORDS

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Introduction

Life has been evolving on the Globe for about 3.5 billion years. Through this vastly long time countless living organisms have been developed. Life conquered all areas of the Earth from the depth of the oceans to the peaks of the high mountains, the deserts, the air, the soil and the water bodies. The huge variegation of niches necessitated the adaptation of biota via differentiation, which resulted in innumerable taxa each operating their complex biochemical pathways.

Dominant discoveries and inventions of cultural, political, economic or scientific nature have always had great impact on the development of human society. Likewise, in the current decades we have been experiencing the revolution of life sciences: we start understanding and exploring the endless potential in utilizing single species, consortia of them or the biochemical processes their lives rely on for our purposes. These discoveries will have a determining effect on various aspects of our lives, such as production of goods, preserving the environment to prevent or cure illnesses, among others. In the current review we introduce some of the most important potential applications of oxygenic photosynthetic microbes, such as cyanobacteria and algae. These organisms have a great wealth of flexible biochemical pathways enabling them to adapt the ever-changing environment.

Due to industrial activity our environment is exposed to dangerous contaminations, which adds to the harmful or toxic compounds of geological origin and are generally regarded as causing increasing health hazard. This concern raises the urgent necessity for the search for new methods of detection of such contaminants and remediation.

Not only the protection of the nature has its high importance but there is also a need for natural products for nutrition, use in healthcare, and other everyday activities. Natural products are mostly more easily accepted by the public than chemically synthesized counterparts, and, on the other hand, the biological production of certain chemicals is also more favourable with respect to technical and economical points of view. Moreover, the organisms, with emphasis on microbes, contain an unexplored wealth of so far unknown molecules that may have therapeutic applications, or serve as nutrients.

The emergence of multidrug resistant cells and pathogens is one prominent reason for the urgent need for new therapeutics.

Cyanobacteria and algae, these oxygenic photosynthetic organisms, are in the focus of research related to all the above-mentioned challenges (Vonshak 1990; Pulz and Gross 2004; Tan 2007; Abed et al. 2009; Richa et al. 2011; Kehr et al. 2011; Costa et al. 2012; Mimouni et al. 2012; Yen et

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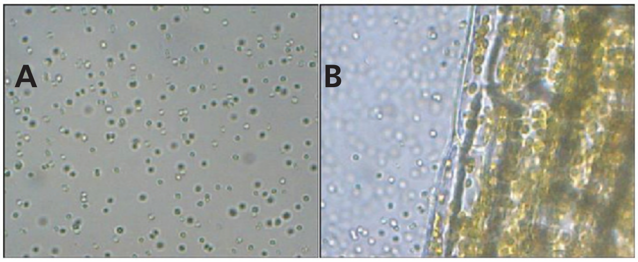

Figure 1. Microscopic view of the unicellular cyanobacterium *Synechocystis* sp. PCC6803 (A) and the chloroplasts from an *Elodea* leaf (B). (A) The photosynthetic model organism *Synechocystis* sp. PCC6803 is a unicellular cyanobacterium of 1 µm in diameter. (B) Note that the morphology of the chloroplasts resembles that of the unicellular cyanobacteria (outside of the leaf) from which they originate. (All photographs were taken by the authors.)

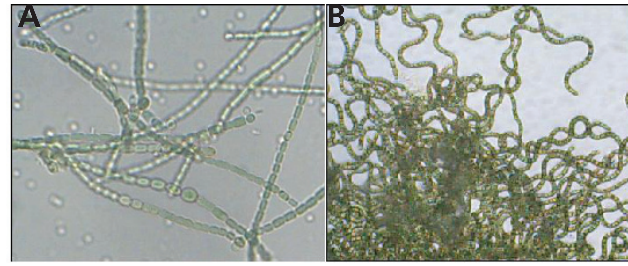

Figure 2. Microscopic view of the filamentous cyanobacterium *Nostoc commune* (A) and *Arthrospira platensis* (*Spirulina*) (B). (A) When grown under nitrogen depletion conditions, some cells will differentiate into larger, rounder specialized cells called heterocysts that are responsible for the N_2 fixation. (B) *Spirulina* cultures are used as dietary supplements for their high protein content and other compounds.

al. 2013; Hoseini et al. 2013; Heydarizadeh et al. 2013; Tan 2013; Raposo et al. 2013; Vinothkumar and Parameswaran 2013; Shalaby 2014).

Organisms

Cyanobacteria

Cyanobacteria are oxygenic photosynthetic bacteria believed to be the ancestor of higher plant plastids (Fig.1). Cyanobacteria can be found in wide range of habitats, that includes freshwater, marine, terrestrial and extreme environments. Their high capability to adapt to various environments could be related to their long evolutionary history. The existence of cyanobacteria more than three billion years ago can be inferred from the stromatolite evidence and some microfossils (Lepot et al. 2008). Cyanobacteria are able to switch between different metabolisms increasing their adaptability; some strains could carry out fermentation, nitrogen fixation or anoxygenic photosynthesis using sulphide as electron donor instead of water molecules (Nagy et al. 2014). The term cyanobacteria includes large number of strains that are all gram-negative bacteria existing as unicellular (Fig. 1A) or as filamentous (Fig. 2) or colonial multicellular forms. Several cyanobacterial strains have been isolated, purified and collected in culture collections (*e.g.*, Pasteur Culture Collection, PCC; American Type Culture Collection, ATCC; Woods Hole Oceanographic Institute Culture Collection, WHOI), but there are still unexplored habitats that could be storehouses of yet unidentified strains. Cyanobacteria are the subjects of various research areas related to their physiology, ecology, morphology or different cellular processes. Many strains are easy to transform and the genomes of several species have been fully sequenced and are publicly available in databases such as CyanoClust (http://cyanoclust.c.u-tokyo.ac.jp/), Kazusa (http://www.kazusa.or.jp/), DOE Joint Genome Institute in the USA (http://www.jgi.doe.gov/), CyanoBase, CYORF (http://cyano.genome.jp/), Cyanosite (http://www-cyanosite.bio.purdue.edu/) among others, facilitating their thorough investigation and genetic manipulation. In recent years cyanobacteria attracted attention because of their potential application in various fields of biotechnology.

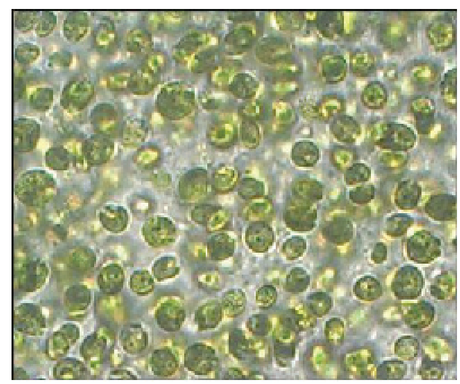

Figure 3. Microscopic view of the unicellular alga *Chlamydomonas reinhardtii*.

Algae

Algae are a large and diverse group of photosynthetic eukaryotic organisms. The probably best-known representatives of algae are the division of green algae (Chlorophyta) such as *Chlamydomonas reinhardtii* (Fig. 3) are unicellular organisms, but this group also includes giant kelps and diatoms. Their chloroplasts originate from endosymbiotic cyanobacteria. As a consequence, they have the same type of oxygenic photosynthesis using two types of photosystems. The habitats and appearances are similar to aquatic cyanobacteria, hence the latter ones were (and sometimes still are) called blue-green algae.

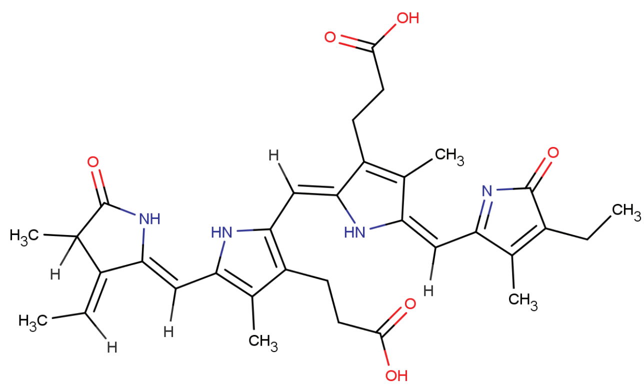

Figure 4. The structure of phycocyanobilin, an important pigment of cyanobacteria. (All structures were drawn using MarvinSketch http://www.chemaxon.com/marvin/sketch/index.php).

Green algae have the potential to be used as fertilizers, biofuel producers, involved in bioremediation and a source of new nutraceuticals and drugs. Their use as nutrients and therapeutics has a long history and even today there is intense research to identify the active compounds from these organisms. They are also favorite targets of biotechnological research. Other genera of algae, like diatoms and the giant kelp, the multicellular brown alga, are similar in many aspects considered here, like the nutritional benefits and biotechnological potentials.

Due to their similar appearance, behavior and potential applications, green algae and cyanobacteria together are commonly referred to as microalgae, a very loosely defined collective term.

Here we introduce some of the most prominent biotechnological applications of cyanobacteria and algae that are directly or indirectly linked to human health conditions. Even seemingly unrelated technologies may have relevant connections: for example poly-hydroxyalkanoates and other fine chemicals can be extracted from cyanobacterial and algal biomass produced in waste-water treatment (Chakravarty et al. 2010; Kumar et al. 2014), which links bioremediation to production of biocompatible surgical implants made of these polymers.

Applications

Basic science

Cyanobacteria as being the ancestors of plastids are good model organisms for photosynthesis studies. Many strains are easy to maintain and the introduction of foreign DNA into the cells can be achieved by various methods such as electroporation, conjugation and also by natural transformation by taking up DNA molecules from the culturing medium, therefore inactivation or introduction of genes involved in production of essential compounds is relatively straightforward. The introduced DNA can be integrated by homologous recombination efficiently, allowing stable insertion into the chromosome. Gene inactivation can be achieved by insertion of antibiotic resistance encoding genes that make possible the selection of the mutant cells (Thiel 1994). In some cases cyanobacteria are more advantageous subjects of research than plants since their maintenance and genetic manipulations is easier and they propagate quickly. Consequently, cyanobacteria are the preferred subject of photosynthesis research (Varkonyi et al. 2002; Cheregi et al. 2007; Kós et al. 2008; Itoh et al. 2012; Kiss et al. 2012), among others.

Another important link of cyanobacteria to basic research is the use of their unique molecules. For example, several restriction enzymes used in molecular biology were isolated from cyanobacterial cells (*e.g.*, *Afl*II, *Afl*III, *Ava*I, *Ava*II, *Avr*II, *Fsp*I, *Nsp*I) (Lyra et al. 2000). There are also cyanobacterial or algal pigments like phycocyanobilin (Fig. 4) that are preferably used as dyes in immune assays or flow cytometry (Oi et al. 1982; Eriksen 2008). Phycobiliproteins covalently bind the phycobilins and efficiently absorb and transfer the light energy with minimal quenching. They can be used as probes for single particle fluorescence imaging applications in clinical and immunological analyses even in combination with green fluorescent probes using simultaneous excitation.

With the advance of molecular biology, genetics and comparative genomics, the metabolic pathway network of an organism can be altered, and virtually any kinds of new pathways can be introduced into an organism. Cyanobacteria, being unicellular prokaryotes are especially suitable subjects for such treatments. There is, however a current public concern about genetically modified organisms and their introduction to the natural environment, and similarly a strong opposition against human consumption of such modified organisms. Therefore, such genetically modified organisms can only be applied as biocatalysts in industrial production of goods and utilization of their gene expression systems coupled with arbitrarily chosen genes or gene clusters. Transcriptional systems (Camsund and Lindblad 2014) can be engineered to reflect environmental stimuli and conditionally express genes.

Biotechnological applications

Pollution control

Biosensors

Our environment is exposed to dangerous contaminations with harmful or toxic compounds due to industrial activity or geological origin that are generally regarded as health hazard. This concern raises the urgent necessity for remediation, the topic of the next section of this paper. The first step is to recognize the existence and assess the level of the pollution, therefore simple and cheap methods are also needed to survey the environment for various pollutants, such as heavy metal contaminations, among others. Cyanobacteria contain effective homeostatic systems for maintaining the intracellular concentration of metal ions (Silver and Phung 1996). The investigation of *Synechocystis* PCC6803 genome revealed the existence of a locus responsible for Zn^{2+}, Co^{2+} and Ni^{2+} resistance. The locus is comprised of three operons each containing a specific transporter and its repressor (Peca et al. 2007). Fusing the repressor and promoter of the corresponding heavy metal exporter with bacterial luciferase genes it is possible to achieve heavy metal concentration dependent expression of these genes. By introducing these constructs to the wild-type cyanobacterial cells, whole cell bioreporter strains can be created (Peca et al. 2008). These cells, when exposed to the corresponding heavy metal solutes start synthesizing the luciferase enzyme, which emits light in a concentration-dependent manner.

This technology enables investigation of single metals, since the promoters show specificity to the elicitors (Blasi et al. 2012), as well as construction of broad range bioreporters by introducing several such constructs in the same cells or by combining several stress-responsive promoters with different reporter molecules. A further possibility is the application of different reporter genes, *e.g.,* in case that fluorescence measurement is more favourable than luminescence the luciferase genes can be exchanged by fluorescent protein coding genes.

It is noteworthy that the efficacy of such systems always depends on the sensitivity of the promoter and the relative expression level of the corresponding genes, that is, the strength of the promoter and the repression rate thereof. Therefore, the selection of the right bacterial strain is always of determining importance for the success of such whole cell bioreporters. For example the *Synechocystis* PCC6803 cyanobacterial strain is not well suited for arsenic sensing, since the concentration that triggers the expression exceeds the required limit (Peca et al. *in press*).

Bioremediation

Algae are efficiently used in wastewater, sewage and agricultural runoff treatment to decrease the dissolved nitrogen and phosphorous containing organic or inorganic compounds. The produced biomass can then be used for various purposes, including soil fertilizer. Algae could also be used for capturing CO_2 if exhaust gases of industrial origin are pumped in the appropriate tank or bioreactor, which speeds up the growth of the culture.

In another type of setup the wastewater flows over sloping surfaces with attached, naturally seeded filamentous algae called algal turf scrubber (ATS) enabling the remediation of millions of litres per day (Mulbry et al. 2008; Adey et al. 2011); a system developed by Adey and co-workers based on the studies on the way how the algae living in coral reefs recycle nutrients of the oceans. Similar algal scrubber is also used as water filtering device in aquariums to remove undesirable chemicals and organic compounds from the water.

Algal species show different sensitivity to environmental pollution therefore changes in the diversity could be a warning sign of deteriorating condition. There is intensive research for application of cyanobacteria in bioremediation of wastewater and also of terrestrial habitats contaminated by industrial effluents (Kumar et al. 2011).

The industrial development, excessive use of chemical fertilizers, herbicides or pesticides and heavy traffic contributed to the increase of other types of environmental pollution, beyond the nitrates and phosphates that may cause eutrophication. The human society has already been aware of the progressive deterioration of the environment and several means of countermeasures have been initiated to reduce or at least slow down the pollution. One of these is the move toward introduction of environment-friendly industrial technologies. Another important action is the bioremediation for reducing the level of the already existing pollution. During bioremediation naturally occurring organisms are used for detoxification (Bonaventura and Johnson 1997).

Industrial effluents pollute drinking water sources; therefore removal of potential toxic contaminants is highly important. Textile and leather industries generate huge volume of effluents, which are usually discharged into surface waters or on land with minimal treatment in India. These effluents often contain high concentration of heavy metals that may have toxic and carcinogenic effect on humans and animals. Several studies indicate that cyanobacterial strains or a consortium of various strains could live in effluent containing water, therefore they could be used for the degradation of chemical compounds. Since some strains are able to transport the heavy metals into the cells, they can be used for heavy metal removal. Studies on effluents indicate that consortia of cyanobacteria and algae can be involved in chromium removal (Kannan et al. 2012) in some cases using resistant strains (Khattar et al. 2007) or non-viable biomass (Gupta and Rastogi 2008).

Lindane, a chlorinated hydrocarbon (Fig. 5A), was used as pesticide for several decades. Its extensive use resulted in contamination of aquatic systems. Due to its possible carcinogenic and mutagenic effects the application of this compound has been prohibited in several countries. Nevertheless, as chlorinated compounds are mostly resistant to biodegradation, their contamination can still be detected in some surface water bodies. *Anabaena* PCC7120, a filamentous cyanobacterium was reported in 1997 to be capable

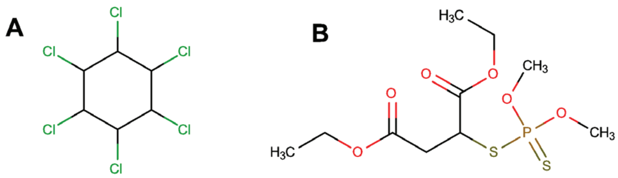

Figure 5. Lindane (A) and malathion (B), two pesticides – causing environmental contamination – that cyanobacteria can be used to remediate.

of dechlorination of this compound (Kuritz et al. 1997). In concert with this finding El-Bestawy and his co-workers aimed to select cyanobacterial strains for the bioremediation of lindane from contaminated lakes. The studied strains also belonged to the order Nostocales, a group of filamentous cyanobacteria, namely: *Anabaena oryzae, Anabaena variabilis* and *Tolypothrix ceytonica*. These strains showed different degree of resistance and some strains seemed to be promising bioremediators, degrading and/or accumulating chlorinated compounds (El-Bestawy et al. 2007; El-Bestawy 2008). Another interesting application of these nitrogen-fixing bacteria is the biodegradation and utilization of malathion (Fig. 5B), an organo-phosphorous pesticide. It was found that *A. oryzae* was capable of utilizing malathion as the sole phosphorus source that renders this technology an efficient and inexpensive tool for the bioremediation of various organo-phosphorus insecticides from contaminated wastewaters (Ibrahim and Essa 2010).

An unfortunate disaster of a nuclear power plant on 11 March 2011 resulted in contamination of the soil with radioactive substances in Tohoku and Kanto districts in Japan. Next year Katoh and co-workers (2012) reported the isolation of a *Nostoc commune* strain and implied its application in field tests. Sasaki and co-workers (2013) investigated the ability of several plant species and of the *Nostoc* strain to decontaminate polluted soil. They found that the terrestrial *N. commune* strain accumulated the radioactive material in high concentration (Sasaki et al. 2013). It seems this strain is able to uptake the radioactive cesium from the soil; therefore it could be used for decontamination.

In concert with these results the potential applications of cyanobacteria are widely investigated for several types of pollution. To date, however, there are reports on large scale application of cyanobacteria in detoxification of pulp-and-paper wastewater (Kirkwood et al. 2005) where the results are still contradictory.

Fertilizers

Soil fertility is a very important factor for agricultural productivity. In order to cope with the increasing global demand for food for the human population either the cultivated land area should be increased, that has its obvious limit, or the soil quality must be improved. Climatic and geographical conditions are not always ideal for agriculture, moreover global warming has adverse effect on agricultural productivity in many countries. This emphasizes the importance of improvement of soil structure and fertility that can be achieved using bio-fertilizers that can increase productivity and in some cases help to maintain the normal soil habitat during intensive agricultural use.

An important factor with this respect is the soluble nitrogen content of the soil. Several cyanobacterial strains are able to fix atmospheric nitrogen. These strains are often filamentous and nitrogen fixation takes place in modified cells, called heterocysts (Fig. 2A), which are unable to divide and photosynthesis is down-regulated in them. Cyanobacteria, including symbiotic strains, can serve as a nitrogen-rich fertilizer needed for crop production (Abd-Alla et al. 1994; Pereira et al. 2008; Osman et al. 2010). In India and Africa several research efforts are made for production of cyanobacterial bio-fertilizers for farmers or even to make them capable to produce their fertilizers by themselves. *Azolla*, an aquatic fern that contains as endosymbiont a nitrogen-fixing cyanobacterium, *Anabaena azollae*, has been successfully used as biofertilizer by rice farmers for more than thousand years (Hasan and Chakrabarti 2009; Bocchi and Malgioglio 2010).

Production of energy sources

With the ever increasing human population there is a growing need for sustained energy supply. As the fossil carbon and fuel sources are limited and will run out soon, new renewable energy sources are sought for. Microalgae contain various types of fatty acids and lipids in their membranes and storage components. While unsaturated fatty acids and especially polyunsaturated fatty acids (PUFA) have higher nutritional benefits, saturated fatty acids are better suited for production of biofuels. Therefore, for biodiesel production it is important to identify and select species that are able to produce high amount of lipids (Huang et al. 2010; Yin et al. 2011; Abou-Shanab et al. 2011; Demirbas 2011; Odlare et al. 2011; Mesquita et al. 2013; Rasoul-Amini et al. 2014) and set up the proper growth conditions for developing cost effective cultivation and harvesting systems (Huang et al. 2010; Karatay and Dönmez 2011; Sánchez et al. 2013). Moreover, genetic engineering is also considered in the development of higher oil production (Radakovits et al. 2010).

Cyanobacteria can also have a role in the production of energy conserving materials such as biofuels, including bioethanol or hydrogen, since due to their photosynthetic performance they can fix CO_2 and use solar energy, their generation time is relatively short and, last but not least, they would not take extensive land area from crop production for agriculture. However, their utilization lags behind that of green algae.

In bioethanol production cyanobacteria can be used indirectly for producing biomass that is the substrate of the fermentation by yeast in a separate downstream process (Su et al. 2013; Mollers et al. 2014; Chow et al. 2014). Cyanobacteria contain high amount of fatty acids. Nevertheless their application for biodiesel (Karatay and Dönmez 2011) is scarce, since in mesophilic conditions they contain relatively high portion of mono polyunsaturated fatty acids (MUFAs) or polyunsaturated fatty acids (PUFAs) rendering them more appropriate for nutritional applications (see below) as compared to diesel oil production, for the latter of which saturated fatty acids from green algae are more suitable. Nevertheless, there are examples of biodiesel oil production in cyanobacteria as well. The main difficulty in hydrogen production is that the hydrogenase (and nitrogenase) enzymes involved in this process are extremely sensitive to oxygen that is produced by these oxygenic photosynthetic organisms in light. There are two roundabouts, however. One is the temporal separation of photosynthetic and anaerobic dark phases (Aryal et al. 2013; Vinh et al. 2013) and the other one is spatial separation of aerobic and anaerobic processes via application of wild type or genetically modified heterocyst forming cyanobacteria (Ow et al. 2009; Mona et al. 2011; Khetkorn et al. 2012).

The same problem arises in hydrogen production using green algae, where the temporal separation is also applicable (Song et al. 2011). An innovative solution of this problem is the co-culture of hydrogen producing green algae and oxygen consuming heterotrophic bacteria that maintain the culture's anaerobic condition even in the light (Lakatos et al. 2014).

Biocompatible polyesters

As we discussed before, nowadays the growing volume of waste disposal is a serious environmental threat. Beyond the chemicals referred to above, the plastics cause one of the most severe problems worldwide. The plastic polymer containers and other wrapping materials made of fossil materials are mostly non-degradable and persist through hundreds of years, defacing lands, rivers and shores, and even forming a "Texas-sized plastic island" off California's west coast (Ryan et al. 2009). The recognition of this problem primed the extensive search for bio-degradable and compostable plastics. Contrary to cyclic polyesters, the linear polyesters are bio-degradable. An increasingly popular representative of such materials is the group of polyhydroxyalkanoates (PHAs), biodegradable polymers produced by bacterial fermentation of sugar or lipids. Although these chemicals are known to be produced using heterotroph bacteria, recent researches revealed that several cyanobacteria can also accumulate polyhydroxyalkanoates,

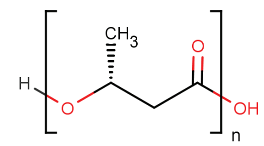

Figure 6. General structure of poly-(R)-3-hydroxybutyrate (P3HB), a polyhydroxyalkanoate of bacterial origin that can be used to produce biodegradable plastics.

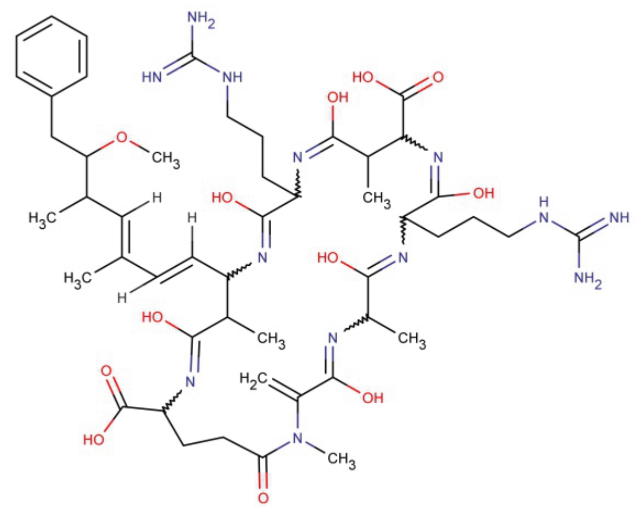

Figure 7. The chemical structure of Cyanoviridin-RR, a cyclic polypeptide from *Nostoc ellipsosporum.*

mainly polyhydroxybutyrate (Fig. 6), when enough carbon sources are available (Abed et al. 2009). Usually, special conditions lead to the PHAs production or accumulation. For example *Spirulina platensis* can produce PHA granules when it is grown in the presence of acetate phototrophically or mixotrophically (Shrivastav et al. 2010). PHAs show similar properties to polypropylene; therefore, they have a potential to be used for biodegradable plastic production. Since they are biocompatible they might be used in medical or pharmaceutical applications, however, their low biodegradation rate limits their possible utilizations (Ulery et al. 2011).

Potentials in medical applications

There is always a need for new compounds that could be used as drug for therapeutics. Cyanobacteria are important targets of research for new pharmaceutical compounds because they produce secondary metabolites with unprecedented chemical structure (Shimizu 2003; Chlipala et al. 2011; Mimouni et al. 2012; Nagarajan et al. 2012; Heydarizadeh et al. 2013). It is noteworthy that many cyanobacterial strains produce toxic compounds (Maruthanayagam et al. 2013). This phenomenon

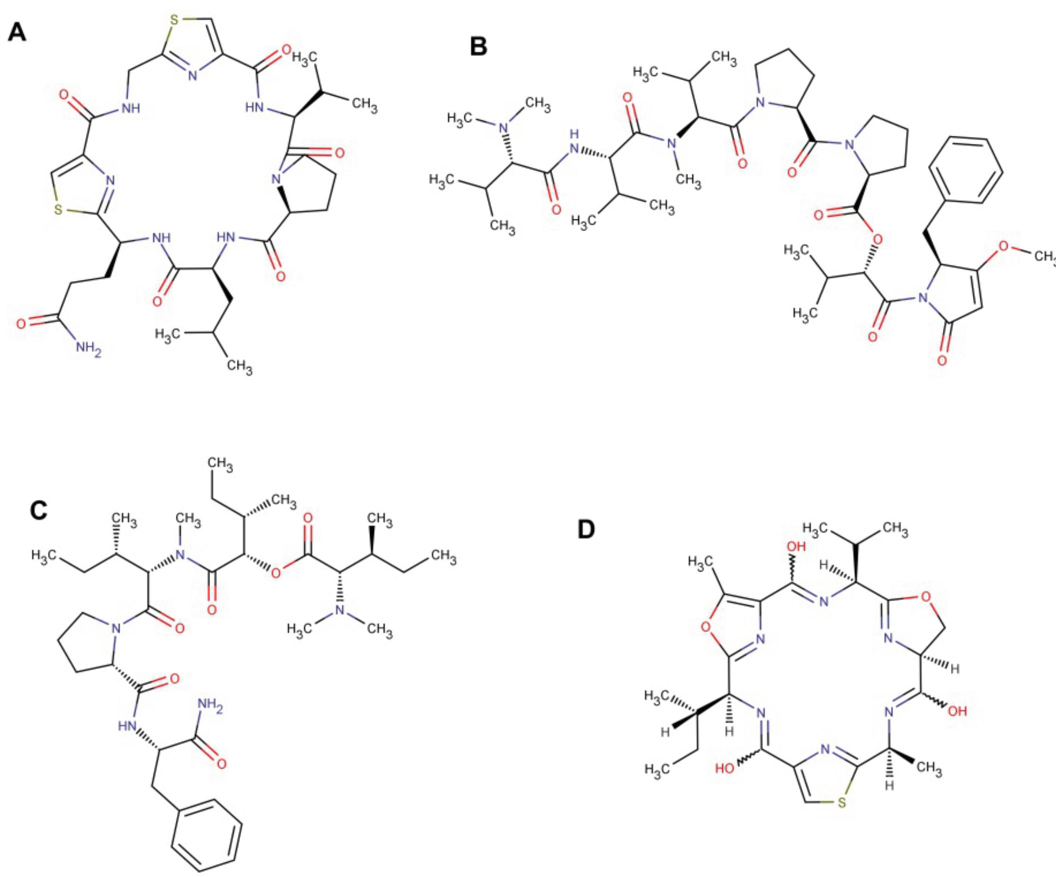

Figure 8. The chemical structures of dolastatin-3 (A), -15 (B), dolastatin-c (C) and -i (D). Dolastatin analogs are used for the treatment of advanced solid tumors.

may cause environmental problems when toxic blooms are formed, and also needs to be considered when producing raw or processed goods for human consumption. Nevertheless, these toxic compounds and their synthetic homologues provide promising tools in search for bioactive compounds. The most thoroughly studied field is that of new compounds with anticancer properties (Costa et al. 2012). The function of these metabolites in the host cells are not known in many cases, but they might be involved in stress response and adaptation. It seems that several enzymes are involved in the assembly of their specific structure, often containing unusual alkyl residues. In the synthesis of these metabolites generally nonribosomal peptide synthetases (NRNPs) and/or polyketide synthetases (PKs) or hybrid NRPS/PK systems are involved (Shimizu 2003). These enzymes may contain several functional domains such as: aminoacid-activating adenylation, peptidyl carrier, condensation, ketosynthase, acyltransferase, ketoreductase, dehydratase, enoyl reductase and acyl carrier protein domains. Identification and characterization of these enzymes or their functional domains have high importance since they could be involved in production of natural product analogues (Whicher et al. 2013).

Peptides and lipid containing metabolites

Hundreds of metabolites were already identified and their number is increasing day by day and their characterization is still in progress. Some families of these metabolites are studied in detail and even their derivatives are under development and analysis. Some interesting examples are as follows:

Cyanoviridin (Fig. 7) is a polypeptide isolated from *Nostoc ellipsosporum.* It was found to have antiviral activity against influenza A virus H1N1, human immunodeficiency virus type (HIV) and Ebola (Botos and Wlodawer 2003; O'Keefe et al. 2003). Cyanovirin showed high binding affinity to viral surface envelope glycoproteins. The discovery of the chemical mode of action (Mori and Boyd 2001; Beutler et al. 2002; Barrientos et al. 2003) and development of suitable expression systems (Mori et al. 2002; Pusch et al. 2005) made it possible to produce mass quantities of this class of

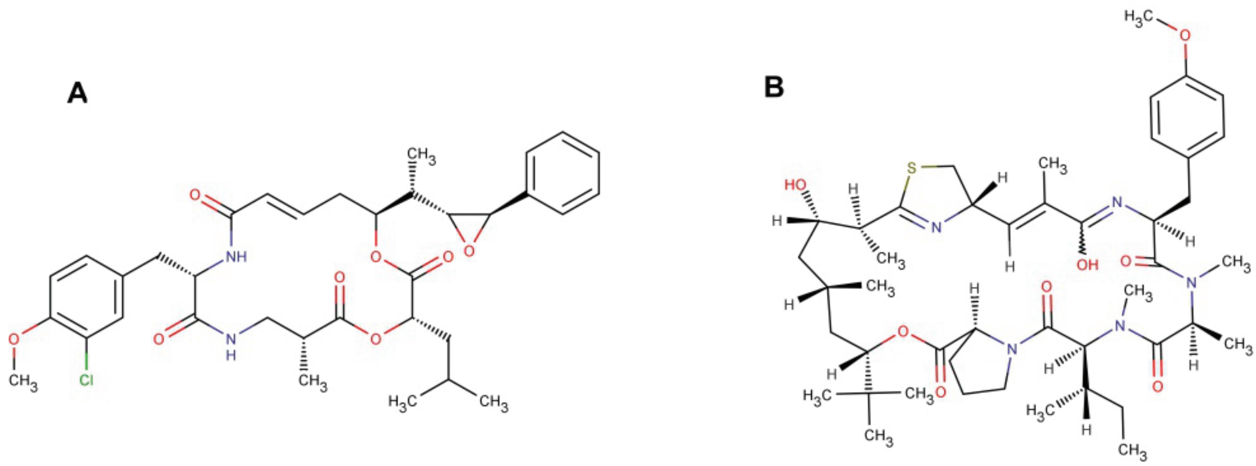

Figure 9. The structures of Cryptophycin-A (A) and apratoxin-A (B), promising candidates for anticancer treatments.

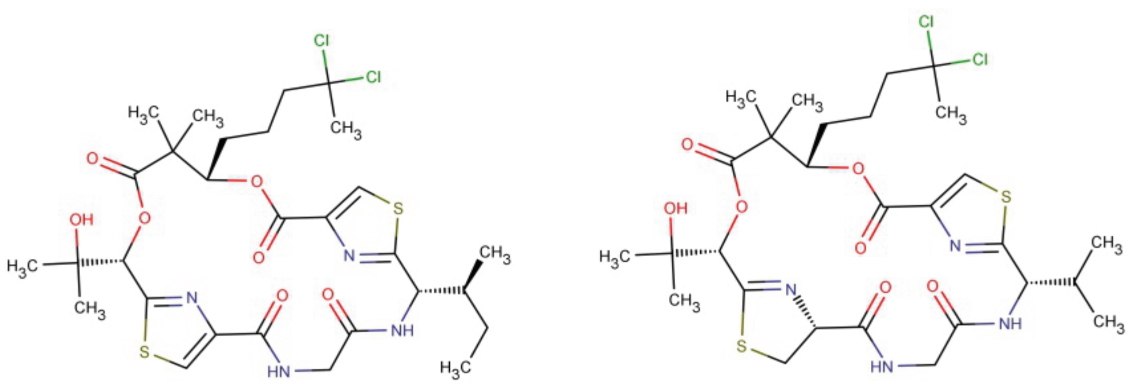

Figure 10. Lyngbyabellin-A and B (left and right, respectively), two cytotoxic compounds from *Lyngbya majuscula*.

compounds enabling their application in practice.

Dolastatin and its analogues (Fig. 8) interact with tubulin and induce apoptosis; they are potent antimitotic, antiproliferative and antifungal compounds (Ali et al. 1998). Phase I and II cancer clinical trials of dolastatin analogues were started (Tamura et al. 2007; Yamamoto et al. 2009; Gianolio et al. 2012). Since dolastatin-10 also showed fungicidal effect it could potentially be used against *Cryptococcus neoformans* in the treatment of immunocompromised patients (Pettit et al. 1998).

Cryptophycin (Fig. 9A), a cyclopeptide isolated from *Nostoc* strains, also acts on microtubule formation and it might be used on solid and multidrug resistant tumor cells (Cells et al. 1994; Smith et al. 1994; Eggen and Georg 2002).

Apratoxin A (Fig. 9B) is a cyanobacterial secondary metabolite, produced via PKS/NRPS pathway. It is a member of the apratoxin family of cytotoxins that are known as a potent cytotoxic marine natural product (Grindberg et al. 2011). This cytotoxin is known for inducing G1-phase cell cycle arrest and apoptosis (Luesch et al. 2001) and it showed promising result on mice in early stage of adenocarcinoma (Nagarajan et al. 2012). Apratoxins contains peptide and also polyketide parts.

Lyngbyabellins (Fig. 10) are lipopeptides consisting of a lipid connected to a peptide and they contain thiazoles and thiazoline heterocycles (Luesch et al. 2000). Lyngbyabellins being cytotoxins could also be potential anticancer agents.

Hectochlorin (Fig. 11 A) structurally resembles the lyngbyabellin family and it shows cytotoxic activity and stimulates actin assembly. It showed antiproliferative activity against various cancer cells (Tan 2007) and antifungal activity against *Candida albicans* (Milligan et al. 2000; Marquez et al. 2002).

Kalkitoxin (Fig. 11B) is highly toxic for fishes and it was demonstrated that it is has an effect on sodium channels. Kalkitoxin is a thiazolin containing lipid that is able to

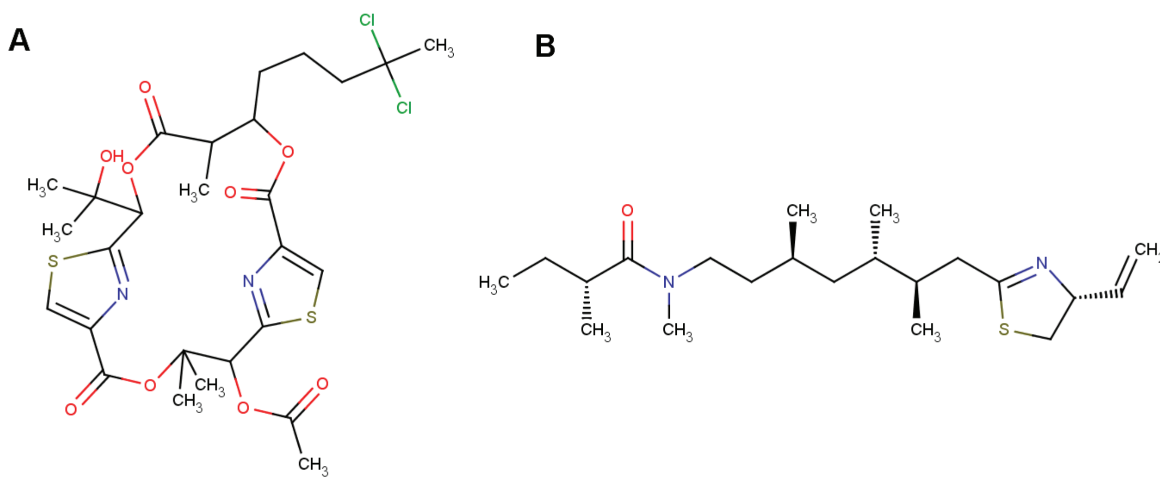

Figure 11. The chemical structures of hectochlorin (A) and kalkitoxin (B), two potent cyanobacterial toxins with medical potential.

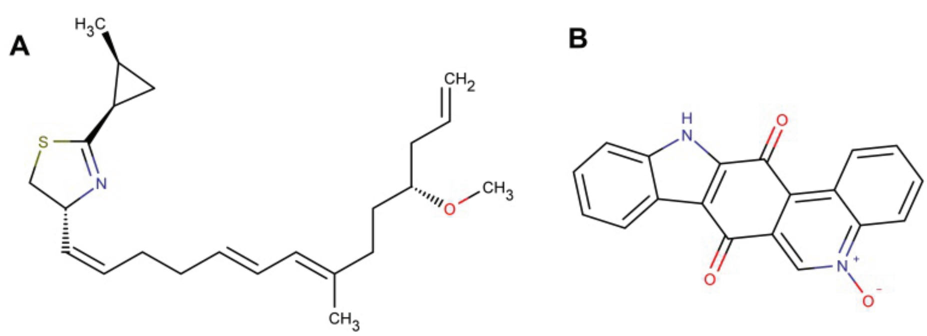

Figure 12. Curacin A (A) and Calothrixin A (B), two cyanobacterial compounds with antimitotic activity on human carcinoma cells, isolated from *Lyngbya majuscula* and *Calothrix* species, respectively.

interact with the neuronal voltage-sensitive sodium channels, therefore it could be involved in the development of neuroprotective drugs (LePage et al. 2005).

Curacin A (Fig. 12A) is a thiazoline- and cyclopropyl ring-containing lipid with potent antiproliferative and antimitotic activity obtained from *Lyngbya majuscula* (Nagle et al. 1995; Chang et al. 2004). It is able to affect tubulin polymerization seemingly through interaction with the colchicine drug binding site on microtubules (Chang et al. 2004).

Calothrixins (Fig. 12B) are also noteworthy components. These molecules are structurally related to quinones and have role in transcription, replication, chromosome condensation and mitosis, which renders them subject of studies in cancer drug development (Khan et al. 2009) and in search for new antibacterial agents (Doan et al. 2001).

UV-protecting compounds

Ozone depletion by anthropogenic gases has increased the atmospheric transmission of solar ultraviolet-B radiation (UV-B, 280-315 nm). It is a serious health hazard being the primary cause of human skin cancer, since UV-B damages most macromolecules in the cell. Their most notably targets are enzymes, resulting in metabolic malfunction; and the DNA, resulting in errors in cell cycle regulation that may eventually lead to continuous cell proliferation, cancer.

As mentioned above, cyanobacteria have appeared on the primordial Earth when oxygen (and hence ozone) was not present in the atmosphere and they were exposed to extremely high doses of solar UV radiation. Several strains still thrive in shallow waters and on terrain, where high UV-B doses are common. Therefore, they evolved and still maintain several ways of diminishing the deleterious effects of UV radiation. They have a complex repair system for the most vulnerable macromolecules (Vass et al. 2013), and they produce molecules that shield the cells from the UV-B (Rastogi et al. 2010; Rastogi et al. 2014). The most prominent such compounds are the scytonemin and the microsporin-like amino acids

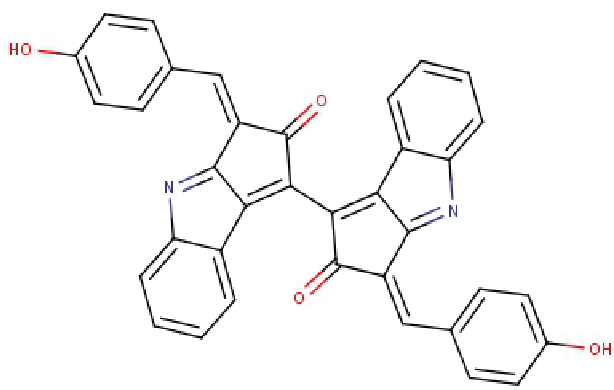

Figure 13. Scytonemin, a biological pigment synthesized by many strains of cyanobacteria.

(MAAs; Rezanka et al. 2004; Ferroni et al. 2010; Rastogi et al. 2010; Rastogi et al. 2014), the latter ones being also present in red algae such as *Porphyra umbilicalis* (Korbee et al. 2005; Blouin et al. 2011).

Scytonemin (Fig. 13) can provide UV protection and it has potential as an anti-inflammation agent (Stevenson et al. 2002). MAAs are used in commercially available cosmetic products like sunscreens and skin lotions, and their anti-inflammatory (Suh et al. 2014) and antioxidant (Rastogi and Incharoensakdi 2014) activity makes them important targets of pharmaceutical research.

Photolyase is a FAD-containing, light-activated flavoenzyme that repairs pyrimidine dimers of UV damaged DNA that was identified also in cyanobacteria (Vass et al. 2013). Application of photolyase with UV filters in liposomes on patients with actinic keratosis and non-melanoma skin cancer improved the confocal appearance of skin after UV light treatment (Puviani et al. 2013), therefore its application in sunscreen products seems promising (Berardesca et al. 2012).

Pigments

Beyond the above mentioned applications in basic science and diagnostics, phycobiliproteins, pigment containing antenna proteins involved in light harvesting in cyanobacteria and some algal genera including red algae, also have features applicable in human medicine. They have antimicrobial, antioxidant, anti-inflammatory, neuroprotective and hepatoprotective properties (Romay et al. 2003; Richa et al. 2011; Abd El-Baky and El-Baroty 2012). Phycobiliproteins were found to exert protection to kidney cells against oxidative stress and cellular damage caused by $HgCl_2$ (Rodriguez-Sanchez et al. 2012). For medical application their large scale production has been developed (Eriksen 2008; Pandey and Pandey 2008).

Chlorophyll is a green pigment found in cyanobacteria and the chloroplasts of algae and plants, up to several hundred molecules per photosystem. Chlorophyll functions in plants to absorb energy from light, making it an extremely important molecule for green photosynthetic organisms. Accordingly, the biological effects and biomedical potentials attributed to this compound trace back to the middle of the last century (Kephart 1955). Application of chlorophyll in cancer diagnostic, prevention and treatment showed quite promising results (Thiyagarajan et al. 2012; Chu et al. 2014; Thiyagarajan et al. 2014).

Cyanobacteria and algae are rich sources of various carotenoids. These molecules have an important role in several cellular processes in their host cells, especially in photosynthesis in which they are involved in light harvesting and in protection from the excess light (Takaichi and Mochimaru 2007; Sozer et al. 2010; Sozer et al. 2011; Takaichi 2011; Domonkos et al. 2013). One of their most important roles is to provide protection from reactive oxygen species, therefore their potential use in human medicine as antioxidant is well known (Christaki et al. 2013). Some of the most recent directions of studies of potential medical applications of carotenoids are as follows.

Beta-carotene is an antioxidant involved in protection from cardiovascular diseases (Zhang et al. 2014). Experiments on mice indicate that beta-carotene rich *Dunaiella* alga diet has a potential to inhibit atherosclerosis progression (Harari et al. 2013). Nevertheless, there are contradicting opinions and results about the effects of beta-carotene in coronary heart diseases and it seems that the differences in carotenoid metabolism might influence the effect of beta-carotene consumption on human health (Tavani and La Vecchia 1999; Siebert and Kruk 2004; Törnwall et al. 2004). Also, the role of carotenoid in cancer treatment and prevention was studied and suggested (Tanaka et al. 2012).

Astaxanthin, lycopene and lutein are carotenoids of medical importance produced, among others in some cyanobacterial and microalgal strains (Del Campo et al. 2004; Liu et al. 2014). Astaxanthin showed promising results in hamster model of oral cancer that suggests it might function as a potent inhibitor of tumor development and progression (Kowshik et al. 2014), although, astaxanthin supplementation did not reduce chemically induced carcinogenesis in rats, rather it seemed to have anti-inflammatory effects (Gal et al. 2012). Lycopene might be able to reduce the risk of cancer and also involved in the prevention of other diseases due to its antioxidant properties effect (Rao and Rao 2007). Carotenoids being antioxidant might prevent lipid peroxidation (Chisté et al. 2014). Lutein supplementation reduces lipid peroxidation and inflammatory response and this way it might protect from cardiovascular diseases (Wang et al. 2013).

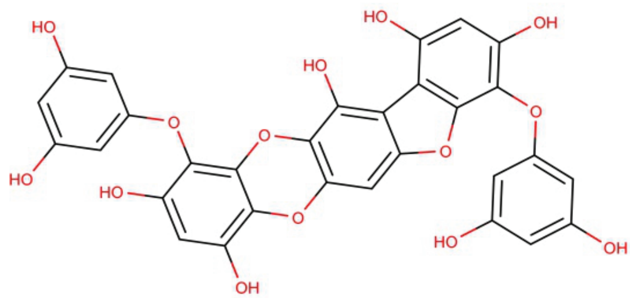

Figure 14. The structure of phlorofucofuroeckol-B, a thoroughly investigated polyphenol of cyanobacterial origin.

Unsaturated fatty acids

Lipid molecules have various roles in living organisms. They serve as structural components of biological membranes and they could also serve as energy source and storing components. In addition they are precursors of other important molecules like vitamins and hormones. Microalgal lipids could be a source of essential PUFAs that cannot be synthesized by humans (Harwood and Guschina 2009; Kagan et al. 2013). The beneficial effects of PUFAs on human health are intensively investigated. PUFAs isolated from marine algae showed anti-inflammatory activity (Ishihara et al. 1998). It seems that PUFAs carry out anti-inflammatory effect by modulating the expression of signal transduction and proinflammatory mediator genes and by suppressing the oxidative stress (Weaver et al. 2009; Chang et al. 2010). Adequate quality and quantity of PUFAs are needed for healthy skin and for the healing of diseased skin by having important role in the structural maintenance and immunologic balance of the epidermis (McCusker and Grant-Kels 2010). PUFAs are also essential for neural development and for the maintenance of the normal functioning (Janssen and Kiliaan 2014).

A wide range of studies indicated the importance of lipids and carotenoids in human health and that algae and cyanobacteria could be a natural source of these molecules. However, more studies are needed for the exploration of the mechanism through which they exert their actions and for discovering how various factors could influence their effects in the human body. More information about the function and health benefit of carotenoids and lipids can be found in the review of Domonkos and coworkers published in this review series (Domonkos et al. 2015).

Phenolic compounds

Polyphenols, the antioxidant compounds that beneficial effects of green tea are attributed to (Yang et al. 2009) are also produced in algae. Antioxidant activity was demonstrated for phenolic substances isolated from marine brown algae (Chkhikvishvili and Ramazanov 2000) and bromophenols isolated from red alga *Vertebrata lanosa* (Olsen et al. 2013). The role in the adaptation to extreme conditions and in the protection of the host cells was also indicated by the increase of these compounds in *Chlamydomonas nivalis* upon UV-C irradiation (Duval et al. 2000). Accordingly, the potential pharmaceutical applications of algal polyphenols utilizing their anti-cancer, photo-aging preventing and anti-inflammatory effects (Thomas and Kim 2011) have been widely investigated.

Phlorotannins can be involved in the fight against human immunodeficiency virus, since they showed inhibitory effect on HIV-1 reverse transcriptase activity (Ahn et al. 2004). Phlorotannins could also be involved in the development of anti-allergic compounds just like phlorofucofuroeckol-B (Fig. 14) showed inhibitory effect on histamine release (Sugiura et al. 2006). Protective effect of phlorotannins against diabetes complication was also suggested (Lee and Jeon 2013). Moreover, phlorotannins showed radioprotective effect by the inhibition of apoptosis via scavenging gamma irradiation induced reactive oxygen species (Shin et al. 2014), another indication of their efficacy in anti-oxidative protection.

Polysaccharides

Polysaccharides are the most abundant macromolecules on Earth, since the tensile fibers of the cell walls of higher plants are made of the polysaccharide cellulose. In most countries starch-containing crops are basic part of the everyday meal. Algae also contain several types of widely used polysaccharides of which the algal origin is nevertheless not so well-known.

Agar, alginates and lectins

Agar is the generic name of seaweed galactants. It has a wide range of applications: it is used as anticoagulant, laxative and bulking agent in suppositories, capsules and tablets. Agar is used in food industry as ingredient for its above mentioned properties and also serves as main component of some delicate national desserts like the Japanese *mizu yokan* and Philippine *halo-halo*, among others. Moreover, agar diet can be used for weight loss of obese people (Maeda et al. 2005).

Alginates are linear polysaccharides composed of linked homopolymer blocks of mannuronic and guluronic acid residues. It is used in medical treatments as a component of products that prevent gastric reflux and alginate fiber dressings are used in the treatment of epidermal and dermal wounds (Draget and Taylor 2011). Monomer composition and sequence arrangement of alginates isolated from different algae could differ which could influence their properties (Skaugrud et al. 1999; Draget et al. 2005). An important therapeutic application of alginate matrix is cell immobilization (d'Ayala et al. 2008). Potential use of alginate in cell transplantation was also suggested, for example insulin-producing cells encapsulated in alginate for diabetes treatment (Skaugrud et al. 1999; Draget and Taylor 2011). The alginate gel could make a barrier between the transplant and the host preventing from undesirable immune system reactions; nevertheless extra care must be taken in such applications as alginate itself may cause immune response (Draget and Taylor 2011). There are also studies on the potential application of alginates in the treatment of patients diagnosed with cystic fibrosis by employing alginates' mucolytic function (Sletmoen et al. 2012). While sodium salt of this polysaccharide is freely soluble in water and it forms a dilute watery liquid, it solidifies within a few seconds or minutes if bivalent cations are added and forms a solid gum. This feature is utilized in cuisine for making jelly and creams, as well as in dentistry as dental impression material.

Not only important carbohydrates, but also carbohydrate-binding proteins, lectins can be found in algae (Cardozo et al. 2007). *In vitro* experiments indicate that algal lectins can help the targeted drug delivery (Singh et al. 2013), which puts them in the focus of biomedical research. Model systems indicated anti-inflammatory effect of algal lectins, which may also be used for prevention of viral transmission due to their capability to bind mannose-containing oligosaccharides on the viral envelopes (Singh et al. 2013).

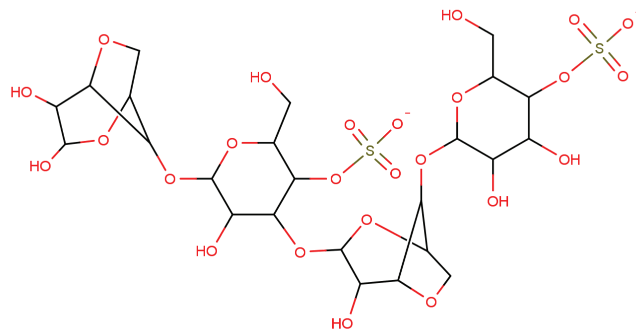

Figure 15. Chemical structure of κ-carrageenan. Carrageenans are sulphated polysaccharides extracted from red algae for their gelling properties used in food industry.

Polysaccharides of red algae

Carrageenans are polysaccharides produced by red algae, consisting of sulfated galactans with alternating backbone. Composition of natural carrageenans could differ significantly. They are widely used in food industry due to their stabilizing, gelling, emulsifying and thickening properties especially in milk products (Cardozo et al. 2007). Carrageenans are mainly classified in three groups: kappa (κ; Fig. 15), iota (ι) and lambda (λ) bearing one, two and three sulfate groups per disaccharide, respectively. Application of carrageenans is often related to these sulfate groups and to their structural diversity (Silva et al. 2010; Silva et al. 2012; de Araújo et al. 2013). There is intensive research on their potential biomedical applications. Anti-tumoral, antiviral, anticoagulant, antifungal and immunomodulatory activities were suggested as well as anti-inflammatory effects (Rodrigues et al. 2012). However it should be mentioned that in some cases biocompatibility was questioned, which may depend on the compound's type and origin. It is also noteworthy that not only they can bind proteins through interaction with sulfate groups but similarly carrageenans are also able to bind heavy metals, which opens their application in contaminated water treatment.

Polysaccharides of green algae

Polysaccharides produced by green algae beside cellulose show high diversity including various sugar composition and sulfate binding. They showed antioxidant, metal chelating, anti-proliferative, anti-tumoral, immune-stimulating and antiviral properties and they are subjects of drug delivery, wound dressing and bone tissue engineering research. One of the best known such polysaccharide is ulvan, mainly composed of rhamnose, xylose and uronic acid units. Ulvans have many useful biological properties for potential application in food and pharmaceutical industry. Ulvan showed anti-oxidant activity depending on the amount and distribution of the sulfate groups (Chiellini and Morelli 2011). Ulvan might be used in anticoagulant therapy due to its heparinoid-like structure. It might have antihyperlipidemic function since it showed interaction with bile acids and based on rat experiments it could reduce the amount of low density lipoprotein cholesterol in serum. Immuno-stimulating and antiviral effects of ulvan are also targets of intensive research. There are also some initial studies on the potential application of ulvan in tissue engineering and wound dressings (Alves et al. 2012; Dash et al. 2014; Popa et al. 2014).

Polysaccharides of brown algae

Brown algae also produce polysaccharides such as alginate, laminarins and fucoidan. Laminarins are storage polysaccharides that modulate the immune response and stimulate the growth of fishes (Yin et al. 2014). Laminarin may be used in anticancer therapies since it has antitumor effects (Ji et al., 2011, 2013; Menshova et al., 2014). Its potential as a dietary fiber was demonstrated on rat experiments (Devillé et al. 2004). Laminarin can be used in wound healing, angiogenesis and atherosclerosis related treatments due to its heparin like properties (Miao et al. 1995) and as such, can have its application even in cancer treatment (Miao et al. 1999). Fucoidan is used in cosmetic, food and biopharmaceutical industries and there is high interest about its potential biomedical application

Figure 16. The *nori* is a red alga, edible seaweed that makes part of the traditional Japanese cuisine.

Figure 17. Commercially available *Spirulina* powder from an Indian manufacturer. According to the label it contains 68% proteins, 12% phycocyanin, 1.5% chlorophyll, 12% carbohydrates, 7% lipids (including ω-3, ω-6 and ω-9 fatty acids), 11% vitamins/minerals/trace elements and 30 mg β-carotene.

in drug delivery, nanomedicine and tissue engineering, due to its anticoagulant, antithrombotic, immune-modulating and anticancer properties (Fukahori et al. 2008; Silva et al. 2012; Wijesinghe and Jeon 2012; Dore et al. 2013; Moghadamtousi et al. 2014; Kwak 2014; Pomin 2014). Fucoidan also showed antiviral properties in mouse experiments against influenza-A virus (Hayashi et al. 2013) and it was suggested that it might be used as anti-HIV agent based on model experiments (Prokofjeva et al. 2013).

Polysaccharides of cyanobacteria

Cyanobacterial polysacharides can have an important impact on our immune system modulation (Tzianabos 2000; Mazmanian and Kasper 2006; Ramberg et al. 2010). Calcium-Spirulan or Calcium spirulinan (Ca-SP), a sulfated polysaccharide isolated from *Spirulina platensis*, showed antiviral activity against HIV-1, herpes simplex type 1 (HSV-1) and influenza-A viruses (Hayashi et al. 1996; Lee et al. 2001) in *in vitro* experiments. Low concentration of Ca-SP prevented HIV-induced syncytium formation. Advantageous features of Ca-SP are the low anticoagulant activity, long half-life in the blood and its dose-dependent bioactivity as it was found in mice studies. The presence of calcium ion seems to be essential for inhibition of cytopathogenic effect and syncytium formation induced by HIV-1. In addition Ca-SP might be used for prevention of tumor cell invasion (Mishima et al. 1998).

Nutritional benefits

As we have shown above, algae and cyanobacteria contain a wealth of valuable compounds enabling industrial scale production of medical drugs, food additives, plastics and fuels, among others. The biological effects were mostly proven using purified compounds. It is also important to emphasize that some strains are edible, therefore tedious and expensive purification steps can omitted, moreover, the metabolites may exert their beneficial effect in a synergistic way. As a consequence, these algal and cyanobacterial strains are widely regarded as healthy food supplements and it is believed that their daily consumption in appropriate doses provide preventive health benefits. With regard to the potent compounds that may cause side-effects when consumed in extreme quantities, it is usually advised that certain daily doses be not exceeded. Some algae are traditional parts of certain national cuisine, like *nori* (Fig. 16), the dried red algal sheets made of *Porphyra yezoensis,* and *Porphyra tenera* used for sushi and several other Japanese foods. Other algae and some cyanobacteria are produced for food supplements due to the growing concern about health problems worldwide. The two species that are produced for this purpose worldwide in the highest quantity are the green alga *Chlorella vulgaris* and the cyanobacterium *Spirulina* (*Arthrospira platensis*; Table 1). Hundreds of shops and web-based suppliers offer various formulations of the dried powders of these organisms and claim their excellent positive effects on the health of the consumers; some of which are scientifically proven. For the combined benefits *Spirulina* (Fig. 17) is frequently referred to as super-food. It contains about 60% proteins (Table 1) with better balanced amino acid content than most plants. Similarly to other cyanobacteria, it is rich in vitamins and moreover it contains various unsaturated fatty acids that themselves make *Spirulina* highly valuable in preventing cardiovascular diseases (Charnock 1999). While short-chain unsaturated fatty acids are produced in plants, the long-chain counterparts are synthesized in cyanobacteria and some algal strains, and traverse the food-chain. Consequently, the widely recognized beneficial effects of fish oil eventually originate from these cyanobacteria. It is also noteworthy that when consumed, these fatty acids are also passed to the offspring. Hence, the roe of marine animals, such as the roe of lumpsucker, hake and salmon, is an excellent source of omega-3 fatty acids (Rincón-Cervera et al. 2009). Similarly, unsaturated fatty acid content of the egg yolk was increased when hens were fed with 3 g/kg *Spirulina* in their diet (Sujatha and Narahari, 2011).

The fatty acid profile of milk was also favourably changed in mammalians upon *Spirulina* supplementation of the fod-

Table 1. Ingredients of dry *Spirulina* and *Chlorella* powder. The amounts in 100 g are shown in masses and as in percent daily values (%DV). The data above are from http://nutritiondata.self.com. Actual amounts may vary depending on supplier and culture conditions.

	Spirulina		Chlorella	
	100 g	%DV	100 g	%DV
Protein	57.5 g	129	58.4 g	117
Total fat	7.7 g	12	9.3 g	14
MUFA	0.7 g	-	-	
PUFA	2.1 g	-	-	
Vitamin A	570 IU	12	51300 IU	1026
Vitamin C	1.0 mg	17	10.4 mg	17
Vitamin E	5 mg	25	1.5 mg	8
Vitamin K	25.5 μg	32	-	-
Thiamin	2.4 mg	159	1.7 mg	113
Riboflavin	3.7 mg	216	4.3 mg	253
Niacin	12.8 mg	64	23.8 mg	119
Vitamin B6	0.4 mg	18	1.4 mg	70
Folate	94 μg	23	94 mg	24
Vitamin B12	0 μg	0	0.1 μg	2
Pantothenic Acid	3.5 mg	35	1.1 mg	11
Choline	66 mg	-	-	-

der (Vahmani et al. 2013; Butler 2014). This finding has two consequences. Firstly, the possible changes in cow and goat fatty acid profile can be altered with forage supplement composition (Maia et al. 2010; Vafa et al. 2012; Shingfield et al. 2013; Yayota et al. 2013; Medeiros et al. 2014), which could then lead to healthier dairy products as an indirect consumption of cyanobacterial fatty acids, just like sea-fish consumption in oceanic coastal regions. On the other hand, as the same principle applies to humans, unsaturated fatty acids in food (supplements) of pregnant and breast-feeding mothers provide these essential fatty acids to the infants (Scholtens et al. 2009; Ribeiro et al. 2012; Urwin et al. 2012; Scholtz et al. 2013). Maternal PUFA and MUFA intake can be important factors affecting breast milk's FA profile (Antonakou et al. 2013). This is especially important as these fatty acids may have positive effect on the development of the body and especially the nervous system (Guxens et al. 2011; Sabel et al. 2012; Scholtz et al. 2013; Janssen and Kiliaan 2014).

Due to the possible side-effects it is commonly advised that the daily dose of an adult should not exceed 3 g or at most 5 g of the dry powder of *Spirulina* and *Chlorella*. Nevertheless, in some rural regions of Africa *Spirulina* is considered the main supply of proteins and consumed in higher amounts as full food, rather than food additive (Vonshak 1990; Belay and Houston 2002) with no reported detrimental effects. It is important to a emphasize that the research on their medical applications is in its infancy and although these microbes present great possibilities, extra care should be taken in order to preclude undesirable contaminations and side-effects of the compounds.

Summary

Cyanobacteria and algae are involved in various applications that could help protecting the environment and diminishing the detrimental effects of our industrial activities. In addition they can be the source of various natural products such as biofuel or biodegradable plastics. Their biomass can also be used in agriculture as bio-fertilizer of lands and as a component of animal feed. They are widely known and used as nutrients or human dietary supplements and in cosmetics. They are a treasury of components that can potentially be involved in biomedical applications. All these can contribute to maintain or recover our health. On the other hand toxin production could pose health hazard for humans and animals alike. Harmful algal blooms have caused severe problem both in marine and freshwater environments. Contamination of the selected strains of cyanobacteria or algae cultured in large-scale for consumption or for metabolite production could also cause problems. It is also very important to set well-defined dosing and to determine the potential side effects in order to assure safety in their application in cosmetics and as dietary supplements. Therefore, appropriate and strict quality control is needed for safe applications of these organisms. For the medical application there are still several open questions and therefore lots of further investigations are needed in order to meet the requirements of the clinical trials before they could be applied. Still, cyanobacteria and algae as well as their metabolites inevitably offer great potentials for our wellbeing.

Acknowledgements

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