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Cyanobacteria and cyanometabolites used in the pharmaceutical and medical industry

Introduction

Cyanobacteria from marine and freshwater habitats are known to produce a diverse array of active compounds (cyanometabolites). These include low molecular weight peptides, polysaccharides, fatty acids, phenols and alkaloids (Burja et al., 2001; Mazur-Marzec et al., 2015). Some of them are a threat to human and environmental health. But many of these natural products possess considerable interest due to their potential applications (Berry et al., 2008; Leão et al., 2012; Almeida et al., 2015). It was estimated that out of the 660 new compounds identified in marine bacteria in the years 1997–2008, till 33% were derived from cyanobacteria (Imhoff et al., 2011). These compounds could be used to obtain commercial algaecides, herbicides, and insecticides. Furthermore, some of these chemical substances demonstrated antifungal, antibacterial, antiviral and even antitumor activity, which could lead to the development of new drugs from them (Berry et al., 2008). Thus, the issue of commercial application of cyanobacteria and their cyanometabolites requires more attention and investigation.

The first discovery of the healing properties of cyanobacteria took place in 1500 B.C. where the *Nostoc* sp. species was used to treat several forms of cancer (Singh et al., 2011). In recent years, many studies have been conducted on the use of cyanobacteria as a potential source of new biologically active substances e.g., microginine, cyanopeptin, aeruginosine and spumigine (Głowacka et al., 2007). The last two can be used to treat hypertension, cardiovascular diseases, and viral infections. In turn, microginine is used to cure hypertension, and cyanopeptin for asthma and viral infections (Singh et al., 2011). Bouillomides A and B from *Lyngbya bouillonii* L.Hoff. & V.Dem. are strong inhibitors of serine protease, elastase, and chymotrypsin (Rubio et al., 2010). Particularly valuable are such compounds that have of antiviral (cyanovirin, scytovirin), antifungal (fischerelin, cryptophycin, calophycin), antibacterial

(microviridine, muscoride, nostocin A), antitumor (apratoxins A and D, dolastine) and antimalar (ambigol C) nature (Wright et al., 2005; Głowacka et al., 2007). In the years 1981–2002, over 60% of anti-cancer and anti-infectious drugs were of natural origin. Currently, due to the high costs of introducing new products to the market by the pharmaceutical industry (500–2000 million dollars), the number of new drugs is decreasing. Currently, drugs are becoming less effective because the resistance of pathogens to antibiotics is increasing. Therefore, it is important to explore new biologically active compounds to produce new drugs (Lam, 2007).

The main aim of this study was to present the knowledge on active compounds of cyanobacteria, which may have potential applications in the pharmaceutical and medical industries. This topic is very important but is still not sufficiently understood. For centuries, human diseases have been treated with natural products because these plant-based, natural drugs are much healthier than their chemical counterparts. In this paper, we showed the positive aspects of cyanobacteria cultivation and possibilities of its commercial use. Algae nomenclature was used here according to *AlgaeBase* (https://www.algaebase.org/) and other microbes from different sources.

Medical and pharmaceutical use of cyanobacteria

Initial knowledge of the properties of cyanobacteria enabled their application on an industrial, pharmaceutical, and medical scale. They produce many biologically active cyanometabolites which have, among others, anticancer, antifungal, antiviral, anti-inflammatory, and antimalarial properties (Gupta et al., 2013; Fig. 1). Cyanobacteria also contain pigments that can strengthen the immune system, and even reduce the risk of heart disease multiple sclerosis, cataracts, and age-related diseases, as well as prevent cancer. Pigments can be used both as medicines and cosmetics, as well as natural pigments for products including ice cream, sweets, soft drinks, and milk products. Extract from blue pigment, which is phycocyanin, obtained from the species of e.g., *Arthrospira* sp., is used in eye shadow, lipsticks and eyeliner. Moreover, this pigment inhibits pancreatic lipase and also, depending on the dose, the growth of Ehrlich cancer cells (El-Baky, 2003). Carotenoids, which are antioxidants, are also anti-cancer drugs substances (Sheih et al., 2009). Chlorophyll together with pigments such as phycocyanin and phycoerythrin have a protective effect against UV radiation on the skin, thus delaying the aging process. In addition, cyanobacteria produce polysaccharides that have the ability to stabilise emulsions and suspensions, form gels, etc., and these can be used in the cosmetics industry as ingredients in nutrients, creams and many other similar products, as well as in the pharmaceutical industry as ingredients in medicines (Głowacka et al., 2007; Tab.1).

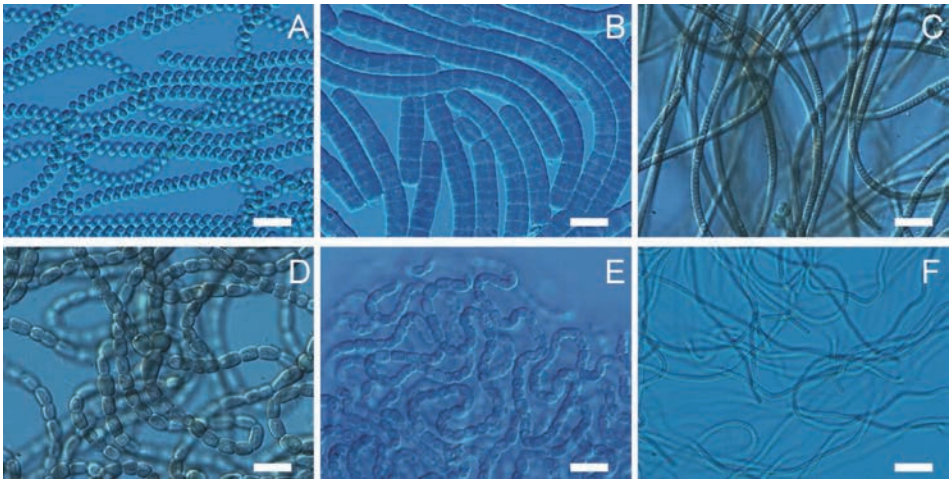

Fig. 1. Examples of cyanobacteria as a potential source for commercial applications: *Arthrospira* sp. (A), *Lyngbya* sp. (B), *Leptolyngbya* sp. (C), *Nostoc* cf. *commune* Vauch. ex Born. & Flah. (D), *Nostoc muscorum* C.Ag. ex Born. & Flah. (E), and *Pseudanabaena* sp. (F). Scale bar = 10 μm (Photo. S. Śliwińska-Wilczewska)

Micro- and macroelements from cyanobacteria

Perhaps, cyanobacteria *Arthrospira platensis* Gomont can be the richest source of vitamins as well as macro- and microelements. They contain nutrients, i.e. *β*-carotene (with antioxidant properties which protect the organism against free radicals), iodine, selenium, zinc, iron, magnesium, manganese, copper and γ-linolenic acid, derived from the group of omega-6 fatty acids, glycolipid H-b2, which is an inhibitor of pancreatic lipase and vitamin B12, which is necessary for the proper functioning of nerve tissue, B1, B2, B3 and E (Klasik et al., 2010; Gupta et al., 2013). Isolated compounds of the *Arthrospira* sp. species have nourishing, strengthening and detoxifying properties, and the extract from its cells has antiallergic, antiviral properties, inhibits carcinogenesis processes, and also reduces blood cholesterol (Głowacka et al., 2007). *Arthrospira* sp. is also rich in proteins – contain their about 60% (Ishimi et al., 2006). It also helps alleviate the occurrence of anemia during pregnancy (Nuhu, 2013).

Cyanobacteria compounds with antiviral activity

Viral diseases, including HIV, affects many people around the world. According to WHO and UNAIDS, 36.7 million people lived with HIV at the end of 2016, of which 1 million died due to it. Thousands of marine organisms, including cyanobacteria, have been tested for antiviral properties (Yasuhara-Bell, Lu, 2010). Such an antiviral compound is cyanovirin produced by *Nostoc ellipsosporum* Rabenh. ex Born. & Flah.

This protein inhibits proliferation of HIV-1, HIV-2, acquired immunodeficiency virus FIV cats and SIV monkeys (Głowacka et al., 2007). Nostoflan polysaccharide from *N. flagelliforme* (Born. & Flah.) Elen. also has activity against the herpes-1 virus (Singh et al., 2011). Scytovirin isolated from the aqueous extract of *Scytonema varium* Kütz. ex Born. & Flah. is also an antiviral protein. It acts similarly to the already mentioned cyanovirin, because both inhibit the process of virus absorption on the surface of host cells. It has been proven that if scitovirin is given up to 8 hours after infection with the virus, it successively prevents the development of infection (Bokesch et al., 2003). In 2002, water extracts from *Arthrospira maxima* Setchell & N.L.Gardner cells were tested and they were shown to inhibit the development of infections caused by the HSV-2 and HSV-1 herpes virus, CMV cytomegalovirus and the virus causing Aujeszky's PRV disease. Polysaccharides produced by cyanobacteria including *A. platensis*, demonstrated the ability to inhibit the replication of HSV, HIV-1, HIV-3, influenza A, and mumps virus, which were cultured in suspensions of human cell cultures (Głowacka et al., 2007). Zainuddin et al. (2002) researched the aqueous and methanolic extract from cyanobacterial cultures of the genus *Calothrix*, *Microcystis*, *Nodularia*, *Oscillatoria*, *Lyngbya* and *Scytonema* to check their activity against influenza A virus in a dog's kidney cells. The most effective extract turned out to be obtained from cyanobacteria of the genus *Microcystis*. A reduction of approximately 90% in viral replication was observed due to protease inhibiting activity. None of the methanol extracts was cytotoxic. Besides, Lau et al. (1993) tested the ability of aqueous cyanobacterial extracts to inhibit reverse transcriptase RT of the avian myeloblastoma virus AMV and HIV and it was proved that 18 (2.0%) extracts showed this possibility in the range of over 50%. On this basis, it was concluded that cyanobacteria can be a promising source of compounds used for viral therapies.

Cyanobacteria compounds with antibacterial activity

Kreitlow et al. (1999) studied hydrophilic and lipophilic extracts of cyanobacteria for their antibacterial activity. In the case of Gram (-) bacteria, no inhibitory activity was found. While for Gram (+) seven species of cyanobacteria from twelve (*Anabaena lemmermannii* P.G.Richt., *A. solitaria* Kleb., *Limnothrix* sp., *Microcystis ichthyoblabe* (G.Kun.) Kütz., *Nodularia* sp., *Oscillatoria rubescens* DC ex Gomont, *O. tenuis* C.Ag. ex Gomont) showed high activity against at least one of the bacteria such as: *Bacillus subtilis* Ehren., *Micrococcus flavus* Cohn and *Staphylococcus aureus* F.J. Rosenbach. In terms of antibacterial activity, Oufdou et al. (2001) tested the benthic species of cyanobacteria *Pseudanabaena* sp. and they showed that the extracts secreted by these organisms inhibited the growth of bacteria *Escherichia coli* T. Esch., *Salmonella* sp. and *Staphylococcus aureus*. In turn, antibacterial activity against *Bacillus cereus* Frank. &

Frank., *Escherichia coli* and *Staphylococcus epidermidis* Evans have a compound called noscomin obtained from *Nostoc commune* Vauch. ex Born. et Flah. (Singh et al., 2011). Gutiérrez et al. (2008) isolated two abietane diterpenes from *Microcoleous lacustris* Desikachary and proved that they showed activity against bacteria *Salmonella typhi* (=*S. enterica* (ex Kauff. & Edw.) Le Minor & Popoff serovar Typhi), *Staphylococcus aureus*, *S. epidermidis* and *Vibrio cholerae* Pacini. Another species of cyanobacteria that produces antimicrobial peptides, including microviridine and cavaguchipeptin is *Microcystis aeuroginosa* Kütz. In addition, antibacterial activity was discovered from muscoride isolated from *Nostoc muscorum* C.Ag. ex Born. & Flah., bastadine from *Anabaena basta*, microsporins from *Nostoc commune*, nostocycline A from *Nostoc* sp. and nostocin A from *N. spongiaeforme* C.Ag. ex Born. & Flah. All these metabolites have antibacterial properties because they can destabilise bacterial cell walls (Głowacka et al., 2007).

Cyanobacteria compounds with antifungal activity

Many cyanobacteria also exhibit properties to inhibit fungal life processes. The methanol extract from *Anabaena solitaria* Kleb. has antifungal activity against *Alternaria alternate* (Fr.) Keissl., *Botrytis cinereal* Pers., and *Colletotrichum gloeosporioides* (Penz.) Penz. & Sacc. Similarly is with cells from cyanobacteria *Nostoc commune*, which, in addition to the fungi mentioned above, also act against *Fusarium oxysporium* Schltdl., *Phytophthora capsica* Leon., *Pythium ultimum* Trow and *Rhizopus stolonifer* (Ehrenb.) Vuill. (Kim, 2006). The anti-fungal activity was also shown by ambigol A and B from *Fischerella ambigua* (Kütz. ex Born. & Flah.) Gomont (Falch et al., 1995), fischerellin from *F. muscicola* Gomont (Srivastava et al., 1998) and tanicolide cryptophycins, and A-D majuskulamides from *Lyngbya majuscula* Harv. ex Gomont (Głowacka et al., 2007).

Cyanobacteria compounds with anti-cancer activity

It was found that some cyanometabolites have apoptotic properties. Such type of action have got, among others, dolastine, which was initially isolated from sea hares (family Aplysiidae), but later it was discovered that it is also produced by cyanobacteria (Costa et al., 2012). Thus, this compound can be used to suppress unnecessary and potentially harmful cells. Dolastine 10, a pentapeptide produced by *Symploca* sp., induces apoptosis of human lymphoblastic leukemia cells (Wall et al., 1999) and also has an inhibitory effect on lung cancer cells (Kalemkerian et al., 1999). Apatoxin D isolated from *Lyngbya* sp. has similar cytotoxic properties concerning lung cancer (Gutiérrez et al., 2008). Apratoxin A, extracted from *L. majuscula* Harv. ex Gomont cells, inhibits bone

sarcoma cancer cells (Liu et al., 2009). Microcyclamide from *Microcystis aeuroginosa* has cytotoxic properties on murine P388 leukemia cells (Ishida et al., 2000). Calothrixin from cyanobacteria *Calothrix* sp. inhibits the growth of HeLa cervical cancer cells (Rickards et al., 1999). Majngulamide C from *Lyngbya majuscula* has inhibitory activity against lung cancer, large intestine cancer and glioblastoma cells (Vijayakumar, Menakha, 2015). Coibamide from *Leptolyngbya* sp. is a cyclic depsipeptide that causes cell cycle inhibition in the G1 phase for MDA-MB-435 breast cancer (Costa et al., 2014). Cryptophycin-1 from *Nostoc linckia* Born. ex Born. & Flah. has a cytotoxic effect on cancer cells of the large intestine, prostate, solid tumors, colon cancer HT-29, Caco-2 and GC3, breast cancer MCF-7 and MDA-MB-231, HeLa cervical cancer, and also leukemia U937, CCRF-CEM and HL-60 (Shih, Teicher, 2001; Singh et al., 2011; Vijayakumar, Menakha, 2015). Nodularins and microcystin from cyanobacteria are toxic inhibitors of protein phosphatases PP1 and PP2A therefore, after appropriate chemical modification they can be used to produce analogues of potential drugs used to inhibit the processes leading to the formation of cancer (Łukomska et al., 2002). Costa et al. (2014) tested the anti-cancer activity of marine cyanobacterial strains. Five of them were the most interesting in terms of bioactive compounds: *Leptolyngbya fragilis* (Gomont) Anag. & Kom., *L. halophila* (Hansgirg) Anag. & Kom., *L. mycoidea* (Frémy) Anag., *Nodosilinea nodulosa* (Z.Li & J.Brand) Perkerson & Casamatta and *Synechocystis salina* Wislouch. It was also shown that two of them – *L. fragilis* and *S. salina* – are the most bioactive against cancer cells.

Cyanobacteria compounds with antiprotozoal activity

Tropical diseases such as malaria, cholera, leishmaniasis, African coma, schistosomiasis caused by protozoa are equally dangerous. According to WHO, over a billion people struggle with one or more of these diseases (Simmons et al., 2008). Cyanobacteria have been found to contain compounds that inhibit protozoa that cause these diseases. Viridamide A is a compound isolated from *Oscillatoria nigrovirdis* Thwaites ex Gomont that acts against *Trypanosoma cruzi* Chagas, *Leishmania mexiana* Garnham, and *Plasmodium falciparum* Schaudinn (Singh et al., 2011). Ambigol C from *Fischerella ambigua* (Kütz. ex Born. & Flah.) Gomont acts against *Trypanosoma rhodesiense* and *P. falciparum* (Wright et al., 2005). In addition, a compound called nostocarboline extracted from *Nostoc* sp. also exhibits activity against protozoa such as *Leishmania donovani* Ross, *P. falciparum*, *Trypanosoma brucei* Plimmer & Bradford and *T. cruzi* Chagas (Singh et al., 2011).

Tab. 1. Examples of cyanobacterial with potential use in medicine and pharmaceutical industry

Cyanobacteria	Effect	References
Arthrospira platensis Gomont	Antiviral activity (HIV type 1, Herpes simplex, Polio)	Głowacka et al. (2007)
Dichothrix baueriana Born. & Flah.	Antiviral activity (Herpes simplex type 2)	Larsen et al. (1994)
Fischerella muscicola Gomont	Fungicides	Hagmann and Jüttner (1996)
Lyngbya lagerheimii (Gomont ex Gomont) Anag. & Kom.	Antiviral activity (HIV type 1)	Gustafson et al. (1989)
Lyngbya sp.	Antitumor activity	Simmons et al. (2005)
Nostoc sp.	Cholinesterase inhibitor (Alzheimer's disease)	Blom et al. (2006)
Oscillatoria agardhii Gomont	Larvicidal activity	Harada et al. (2000)
Phormidium tenue Gomont	Antiviral activity (HIV type 1)	Gustafson et al. (1989)
Phormidium sp.	Fungicides (oral candidiasis)	Garima et al. (2013)
Pseudoanabaena sp.	Antibacterial activity (*E. coli*, *Salmonella* sp.)	Głowacka et al. (2007)
Scytonema ocellatum Lyngb. ex Born. & Flah.	Fungicides	Patterson and Bolis (1995)
Symploca hydnoides Kütz. ex Gomont	Antiparasitic activity (malaria, Chagas disease)	Linington et al. (2008)
Westiellopsis sp.	Larvicidal activity (malaria, meningitis)	Rao et al. (1999)

Conclusions

Cyanobacteria have a wide range of occurrences and occupy many habitats, including oceanic areas, freshwater lakes, and even extreme habitats such as deserts, coastal rocks, glacial lakes or hot springs. In eutrophic and hypertrophic waters, cyanobacteria often dominate the phytoplankton in the summer period, creating a massive and harmful bloom. Some cyanobacteria produce toxins that can significantly affect human health. However, even though cyanobacteria contain toxic substances, there are species whose secreted organic compounds can be used as a potential source for commercial applications. The properties of cyanobacteria discussed in this work emphasize how these organisms can be potentially used by humans in many areas of their life. Cyanometabolites can serve as drugs for incurable diseases such as cancer or other diseases caused by bacteria, viruses, fungi or protozoa. However, the composition and functional role of many cyanometabolites remain unknown, therefore, the issue of commercial application of cyanobacteria and their cyanometabolites require more attention and investigation.

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Conflict of interest

The author declares no conflict of interest related to this article.

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Cyjanobakterie i cyjanometabolity stosowane w przemyśle farmaceutycznym oraz medycznym

Streszczenie

Związki bioaktywne sinic wykazują różnorodne właściwości, które potencjalnie mogą być wykorzystane w wielu sektorach przemysłu. W artykule tym szczególny nacisk położono na wykorzystanie sinic i ich cyjanometabolitów, zarówno w przemyśle farmaceutycznym, jak i medycznym. Scharakteryzowano związki wyizolowane ze szczepów sinic, które można stosować do wytwarzania leków o działaniu przeciwwirusowym, przeciwgrzybiczym, przeciwnowotworowym, przeciwdrobnoustrojowym oraz przeciwbakteryjnym. Pokazano również pozytywne aspekty hodowli sinic i możliwości ich komercyjnego wykorzystania.

Key words: applications, blue-green algae, cyanobacteria, cyanometabolites, industry

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