ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Issue 2, 2014

ISSN - 0974-2441

Research article

HARVESTING OF VALUABLE ENO- AND EXO-METABOLITES FORM CYANOBACTERIA: A POTENTIAL SOURCE

MAHEEP KUMAR

Department of Botany, Guru Ghasidas Vishwavidyalaya. Email: maheep.bot@gmail.com.

Received: 23 November 2013, Revised and Accepted: 2 January 2014

ABSTRACT

Most of the disease is growing resistace from thr applied drugs. However, in this view people search for cheap and effective drugs for their cure. Cyanobacteria in this respect can help in curing disease with cheap and effective manner. Cyanobacteria are photosynthetic prokaryotic microorganism. From ancient time cyanobacteria were used as food and fodder. However, it is notorious for toxin production and fouling of ponds as it form water bloom. Now-a-days various studies have done to prove its potency in medical science also. They produce various metabolites that are antibacterial, antifungal, antimalarial, anticancerous, antitumor, antialgal, antiviral, UV protectants, inhibitors of enzymes, hepatotoxins and neurotoxins. These metabolites produced at the particular cell age and are regulated by various biotic and abiotic factors. Many cyanobacteria produce compounds with potent biological activities.This review aims to showcase of cyanobacterial secondary metabolites with a comprehensive coverage of antibacterial, antifungal and other activity of cyanobacteria.

Keywords: Cyanobacteria·Organic extract· Secondary metabolites· Antimicrobial· Bioactive compounds.

INTRODUCTION

Natural products which have no role in growth and reproduction are largely referred as secondary metabolites. They are formed on the basis of precursor substances participating in primary metabolism, such as acetic acid, amino acids, glucose and are observed mainly as final products of biochemical transformations. Secondary metabolites are quite diverse by its chemical structures. It included steroids, terpenoids, alkaloids, polyketides, phenolic metabolites, carbohydrates, lipids and peptides. They can be classified on the basis of their biological functions as hormones, antibiotics, toxins, pheromones, etc. and are found to be the most productive source of leads/active compounds for the development of drugs, over a 100 new products are in clinical development, particularly as anti-cancerous agents and anti-infective. Use of advance techniques increases the availability of novel drugs that are produced in bacteria or actinomycetes or yeast [1]. Most of drugs available in the market are Actinomycetes, Bacterial and fungal origin. With the discovery new drugs, drug resistance among the target organism also emerged as; methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* [2-4]. This indicates the loss of efficacy of conventional antibiotics and necessitates for their replacement with new generation drugs. These all lead to search about the new drugs and perhaps the new sources because there are a large number of untapped microbes which produces good and potent bioactive compound. In this respects cyanobacterial origin has most important because in the microbial diversity (10^6-10^7) only 1-10% of cultured bacteria (2×10^5) has been unexplored and the natural products from cyanobacteria, actinomycetes and uncultured bacteria are likely to offer newer source of antibiotics [5,6].

Cyanobacteria are photosynthetic, oxygen evolving prokaryotes found in every corner of world including the extreme condition. Since decades Cyanobacteria have been found to be the potent source of antibacterial, antifungal, anticancerous, antiviral and antiprotozonal [7-9]. They produced bioactive compounds in two way either within the cell biomass *i.e. endo*-metabolites and towards the environments *i.e. exo*-metabolites. A large number of bioactive secondary *endo*-metabolites have been isolated from cyanobacteria such as lyngbyabellin from *Lyngbya majuscula* (cytotoxic) pahayokolide A from *Lyngbya semiplena* (anticancer), hapalindole series (antituberculosis), venturamide A, B from *Oscillatoria* sp. (antimalarial), Antimalarial linear lipopeptides from marine cyanobacterium *L. majuscula* (antimalarial) [10-14].Thus cyanobacteria produce a large number of diverse natures of compound and their property depends upon their habitat and species.

A single cyanobacterium may possess one activity or several activities depending upon its screening, and the production of bioactive compounds depends upon the various biotic and abiotic factors [15, 16].

ORGANIC EXTRACTS ACTIVITY

The biomass of cyanobacteria shows bioactivity when extracted in organic solvents. Methanolic extracts from *Tychonema bourrellyi, Aphanizomenon flos-aquae* and *Cylindrospermopsis raciborskii* and also the aqueous counterpart from *Microcystis aeruginosa* and *T. bourrellyi*, were significantly antibacterial [17]. The methanolic extract of *Chroococcus dispersus* has Antifungal and antituberculosis activity [18]. The chloroform and methanol extracts of *Hapalosiphon* were antimycobacterial [19]. Bioassays of methanolic extracts from the genera of *Anabaena* and *Nostoc,* were found antifungal and antibacterial [20]. Methanolic extracts of *Oscillatoria* sp. (halo-tolerant) showed inhibition against fungal pathogens, followed by extracts in n-propanol, petroleum ether and water [21]. Extractions of bioactive compounds from *Phormidium* sp. in different solvents (hexane, ethanol and water) were found antifungal and antibacterial [22].

Polar (water) and non-polar (ethyl acetate) extracts from the hot spring cyanobacterial layer tested for their antibacterial, anti-diatom and quorum sensing inhibitory activities under natural conditions, proved antibacterial [23]. Antimicrobial activity of ethanol, acetone and methanol, extracts of *O. latevirens, Chrococcus minor* and *M. aeroginosa* on Gram-positive and Gram-negative organisms was also observed were antifungal [24]. The strains *Cylindrospermopsis raciborskii*, *Synechococcus elongatus*, *M. aeruginosa*, *M. panniformis* and *Fischerella* sp. provided the most active extracts [25]. The organic solvent extracts of *Oscillatoria subrevis* and *O. amphibia* in pyridine, n-butanol showed activity against the five *Vibrio* pathogens [26]. *Anabaena* supernatants and ethanolic extracts found antimicrobial activity [27]. The ethanol extracts of *Phormidium* sp. and *Microcoleus* sp. at various concentrations were activite against *Streptococcus enteritidis* and *E. coli* [28].

ENDO-METABOLITES and ACTIVITY

Various endo-metabolites from cyanobacteria have been identified as linear peptide from the dragonamide series was isolated, along

with the two known modified linear peptides, dragonamide A and herbamide B [29]. A number of anti-infective compounds against the neglected diseases include viridamides A and B, gallinamide A, dragonamide E, and the almiramides identified from marine cyanobacteria [30]. N-methylated linear lipopeptides, almiramides A-C from *L. majuscula* were active against *Leshmania donovani* [31]. Two cyclic peptides, anabaenopeptins A and B, were isolated as a third group of bioactive compounds from *Anabaena flos-aquae* [32]. Five new antibacterial ambiguine K-O isonitriles and nine previously described indole alkaloids were isolated from the cultured cyanobacterium *Fischerella ambigua* [33]. Two depsipeptide metabolites, scyptolin A and B, a least antimicrobial compound were reported recently from terrestrial cyanobacterium *Scytonema hofmanni* [34]. Four novel cyclic undecapeptides, antimicrobial, lyngbyazothrins A, B, C, and D, were isolated from the cultured *Lyngbya* sp. as binary mixtures [35]. New natural products 3,5-bis (2,4-dichlo rophenoxy)-2,6-dichlorophenol (ambigol C), a highly chlorinated aromatic compound, and 2,4-dichlorobenzoic acid were isolated from the terrestrial cyanobacterium *Fischerella ambigua* together with the known compounds ambigol A and tjipanazole D, Ambigol C has moderate activity against *Trypanosoma rhodesiense* [36]. A novel acetylene-containing para-14-cyclophane, nostocyclyne A, possessing antimicrobial activity, is the major active metabolite of the natural bloom of the cyanobacterium *Nostoc* sp. [37]. Viridamide A isolated from a marine strain *Oscillatoria nigro-Viridis* showed antitrypanosomal activity and antileishmanial activity [38]. Gallinamide A isolated from *Schizothrix* species showed potent initial antimalarial activity against the *Plasmodium falciparum* [13]. Venturamides A and B were isolated from the marine cyanobacterium *Oscillatoria* sp. has antimalarial [39]. Among the other secondary metabolites, lobocyclamide A-C a lopopeptide from *L. confervoides* showed moderately antifungal [40]. The cryptophycin from *Nostoc* was antifungal, antimicrobial and insecticidal but not antibacterial [41]. Anachelin H an antimicrobial compound from *Anabaena cylindrica*, had moderate activity against bacterial and fungal pathogens [18]. *Microcoleous lacustris* yielded two abietane diterpenes, 20-nor-3a-acetoxyabieta- 5,7,9,11,13-pentaene and 20-nor-3a-acetoxy-12- hydroxy-abieta-5,7,9,11,13-pentaene that when assayed were active against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella typhi*, and *Vibrio cholerae* [42]. Scytoscalarol, an antimicrobial sesterterpene bearing a guanidino group, was isolated from the cultured cyanobacterium *Scytonema* sp. was active against *Bacillus anthracis*, *S. aureus*, *Escherichia coli*, *Candida albicans* and *Mycobacterium tuberculosis* [33]. Four novel cyclic undecapeptides, lyngbyazothrins A, B, C, and D were isolated from the cultured *Lyngbya* sp. were active against *Micrococcus flavus Bacillus subtilis*, *Escherichia coli*, *P. aeruginosa*, and *S. marcescens* [35]. A number of endo-metabolites as hapalindole A, C, G, H, I, J, and U, hapalonamide H, anhydrohapaloxindole A, and fischerindole L have been isolated from cyanobacteria [43].These are the *endo*-metabolites which is isolated through the extraction of cell biomass in suitable solvents.

EXO-METABOLITE and ACTIVITY

The other bioactive compound such as *exo*-metabolites are isolated through the cell free extract such as a new brominated indole alkaloid, designated as bromoanaindolone, was isolated from the culture media of the cyanobacterium *Anabaena constricta* and was identified as 6-bromo-3-hydroxy-3-methyl-indol-2-one. This extracellular metabolite of *A. constricta* possessed antimicrobial (anticyanobacterial and antibacterial) activity [44]. Two cytotoxic and non-cytotoxic compounds 4,4′-dihydroxybiphenyl (I), two more compounds, the β-carboline 9H-pyrido(3,4-b) indole (norharmane, II) and N,N′-(4,5-dimethyl-1,2-phenylene)bis-acetamide (III), were discovered from exometabolite of *Nostoc insulare* [45]. Two known cyanobacterial exometabolites 4,4-dihydroxybiphenyl and norharmane (9H-pyrido(3,4-b)indole) and in addition of harmane (1-methyl-9H-pyrido(3,4-b)indole) were isolated from cyanobacterium *Nodularia harveyana* posses antialgal activity [46].

A new brominated indole alkaloid, bromoanaindolone, was isolated from culture media of *A. constricta* and identified as 6-bromo-3-hydroxy-3-methyl-indol-2-one. This extracellular metabolite was antimicrobial (anticyanobacterial and antibacterial) for different test systems, such as suspension and porous matrix and the molecular structure elucidated on the basis of IR, MS and NMR data [45]. Exopolysacharides of unicellular cyanobacterium *A. halophytica* [47], and lipophilic extracts of *F. ambigua* led to the isolation of three compounds ambigols A and B, and tjipanazole D [48]. Among these, ambigols A and B were antibacterial, antifungal, cytotoxic, mollusccidal, anti-inflammatory and antiviral. Tjipanazole D on the contrary, was the moderate antibacterial. Noscomin, the novel extracellular metabolite with the diterpenoid skeleton, was active against *B. cereus, S. epidermidis* and *E. coli* [49]. Norharmane (9H-pyrido(3,4-b) indole) from *Nodularia herveyana* and 4,4'-dihydroxybiphenyl from *Nostoc insulare* are the two exometabolites with anticyanobacterial, antibacterial and antifungal activity [46].

OTHER ACTIVITY

Besides antimicrobial compounds, cyanobacteria possess most of the other activity which includes cytotoxic, anticancerous, antituborculosis, antialgal, antiviral and many more.

N-methylwelwitindolinone C isothyocyanate from *H. welwitschii* UH IC-52-3 and *Westiella intricata* UH HT-29-1 (*Stigonemataceae*), was responsible for MDR reversal and also the insecticidal activity, respectively [50]. Borophycin, the potent cyanotoxin, was also isolated from the marine strain of *N. linckia* [51]. A number of cyanobacteria and a very few other microalgae, have been screened for antiviral activity so far, but the limited results available are promising [52]. Microcystin, the first metabolite whose non-ribosomal biosynthesis was confirmed by knock-out mutagenesis, is the worldwide common cyanobacterial hepatotoxin [53]. The lipid extract of the marine *L. majuscula* was toxic to the mollusc *Biomphalaria glabrata* [54]. Subsequent bioassay-guided fractionation of this extract yielded the novel lipopeptide, barbamide, as the active compound. Cyanovirin-N from *N. ellisposporum* was also anti-HIV [55]. Oscillapeptin D from *O. agardhii*, was the trypsin inhibitor [56].

Cyanobacteria are also the source of antialgal agents as *M. aeruginosa* caused complete inhibition of growth and cell lysis in *N. muscorum* and *Anabaena* [57]. The freshwater cyanobacterium *N. spongiaeforme*, released violet pigment nostocine A in the ambient medium that was growth inhibitory to several microalgae compared to parquat [58]. *Nostoc* 78-12A is the source of a new quaternary β-carboline alkaloid, nostocarboline, the inhibitor of butyrylcholineesterase (BchE) relative to galanthiamine, the drug approved for treatment of Alzheimers's disease [59].

Cyanobacteria are also the ideal source of anticancerous/antiviral agents. Exopolysacharide (EPS) from the unicellular cyanobacterium *A. halophytica* was effective against influenza virus A FM (H1N1) (FM1) in mice [60]. *N. insulare* produced only the non-toxic N,N'-(4,5-dimethyl-1,2-phenylene) bis-acetamide during linear growth while in stationary, it shifted to antimicrobial and cytotoxic exometabolites, 4,4'-dihydroxybiphenyl and 9H-pyrido (3,4-b) indole (norharmane) [44]. Among the 54 *Nostoc* strains screened for acetylcholinesterase inhibition, the efficacy varied in a strain specific manner [61]. The trypsin inhibitor, cyanopeptolin was also isolated from the freshwater *Aphanocapsa* sp. [62], while aqueous or organic extracts of *Phormidium* sp. were antioxidants [63]. Grassypeptolide, a new anticancerous compound has been reported from *L. confervoides* [64]. The novel peptide cytotoxin 'bisebromoamide' from marine *Lyngbya* sp. was also isolated [65]. This also opens new strategies for the development of novel neurochemicals from cyanobacteria. The organic extracts of *Schizothrix* sp. from a tropical reef near Piedras Gallinas (Caribbean coast of Panama) were antimalarial with particular reference to W2 chloroquine-resistant *Plasmodium falciparum* [13]. A novel antiprotozonal compound, Viridamide A was isolated from cyanobacteria [66]. The cell extract of terrestrial *Nostoc* sp. (UIC 10062), displayed antiproliferative activity against the HT-29 human colon cancer cell line [67].

Thus, Cyanobacteria are an important and little explored microbial resource offering novel secondary metabolites for lead compounds and discovery of newer drugs. Cyanobacteria produce a wide variety of toxins and other biomedically interesting bioactive compounds. They produce cyclic heptapeptide hepatotoxins, microcystins and

pentapeptide nodularins and antitumor, antiviral and antifungal compounds. Many of the pharmaceutically interesting compounds in cyanobacteria are peptides, including cyanobacterial toxins and important candidates for anti-cancer drugs. Peptide synthetases common in cyanobacteria, are responsible for the production of cyanobacterial hepatotoxins and other peptides.

CONCLUSIONS

Microbial natural products are the important source of new drugs. Among the producers of commercially important metabolites, cyanobacteria have proven to be the prolific source with a surprisingly small group of taxa accounting for the vast majority of compounds discovered till date. Cyanobacteria are one of the richest sources of known and unknown bioactive secondary metabolite is unquestionable. Many compounds from cyanobacteria could be useful for welfare of mankind if proper investigation done. Because of high discovery rate, research should be done to discover other beneficial of cyanobacteria. Cyanobacteria are a simple, but primitive and diverse group of microorganisms, with characteristics in common to both bacteria and algae. Their success as a group in a wide range of habitats has been attributed to their unique physiological characters and high adaptive ability under a wide range of environmental conditions. This compilation reviews the salient advances in the discovery of bioactive compounds from cyanobacteria and their significance in agriculture and industry.In addition to the procurement of marine cyanobacteria from unexplored locales, the amenability of field collected strains to laboratory culture is an important factor in the drug discovery process.

REFERENCES

1. Harvey AL Natural products in drug discovery. Drug Discovery Today 2008; 19/20(13): 894-901.
2. Reynolds R, Potz N, Colman M, Williams A, Livermore D, MacGowan A. Antimicrobial susceptibility of the pathogens of bacteraemia in the UK and Ireland 2001-2002: the BSAC bacteraemia resistance surveillance programme. Journal of Antimicrobial Chemotherapy 2004; 53: 1018-1032.
3. Karchmer AW. Increased antibiotic resistance in respiratory tract pathogens: PROTEKT US- an update. Clinical Infectious Disease 2004; 39: 142-150.
4. Paterson DL. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. Clinical Infectious Disease 2006; 43: 43-48.
5. Cowan DA. Microbial genomes: the untapped resource. Trends in Biotechnology 2000; 18: 14-16.
6. Clardy J, Fischbach MA, Walsh CT. New antibiotics from bacterial natural products. Natural Biotechnology 2006; 24: 1541–1550.
7. Kumar M, Tripathi MK, Srivastava A, Nath G, Asthana RK. A Comparative Study of Antibacterial Activity of Brackish and Fresh Water Cyanobacterial Strains. Asian Journal of Experimental Biological Sciences 2012; 3(3):548-552.
8. Kumar M, Tripathi MK, Srivastava A, Gour JK, Singh RK, Tilak R, Asthana RK. Cyanobacteria, *Lyngbya aestuarii* and *Aphanothece bullosa* as antifungal and antileishmanial drug resources. Asian Pacific Journal of Tropical Biomedicine 2013; 3(6): 458-463.
9. Kumar M. *Lyngbya* sp. : a suitable cyanobacterium for harvesting antimicrobial compounds. Asian Journal of Pharmaceutical Clinical Reseasrch 2014; 7(1): 6-9.
10. Han B, McPhail KL, Gross H, Goeger DE, Mooberry SL, GerwickWH. Isolation and structure of five lyngbyabellin derivatives from a Papua New Guinea collection of the marine cyanobacterium *Lyngbya majuscula*, Tetrahedron 2005; 61: 11723-11729.
11. Berry JP, Gantar M, Gawley RE, Wang M, Rein KS. Pharmacology and toxicology of pahayokolide A, a bioactive metabolite from a freshwater species of *Lyngbya* isolated from the Florida Everglades. Comparative Biochemisty & Physiology 2004; 139: 231–238.
12. Mayer AMS, Rodriguez AD, Berlinck RGS, Hamann MT Marine phar- macology in 2005–6: Marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other misce- llaneous mechanisms of action. Biochimica Biophysica Acta 2009; 1790: 283-308.
13. Linington RG, Clark BR, Trimble EE, Almanza A, Ureña LD, Kyle DE, Gerwick WH Antimalarial peptides from marine cyanobacteria: isolation and structural elucidation of gallinamide A. Journal of Natural Product 2009; 72: 14-17.
14. McPhail KL, Correa J, Linington RG, González J, Ortega-Barría E, Capson TL, Gerwick WH. Antimalarial linear lipopeptides from a Panamanian strain of marine cyanobacterium Lygbya majuscule. Journal of Natural Product 2007; 70: 984-988.
15. Sivonen K. Effects of Light, Temperature, Nitrate, Orthophosphate, and Bacteria on Growth of and Hepatotoxin Production by Oscillatoria agardhii Strains. Appl Environ Microbiol 1990; 2658-2666.
16. Granéli E, Flynn K. Chemical and Physical Factors Influencing Toxin Content. Ecological Study 2006; 189: 229-241
17. Østensvik Ø, Skulberg OM, Underdal B, Hormazabal V. Antibacterial properties of extracts from selected planktonic freshwater cyanobacteria – a comparative study of bacterial bioassays. Journal of Applied Microbiology 1998; 84, 1117–1124.
18. Ghasemi Y, Moradian A, Mohagheghzadeh A, Shokravi S, Morowvat MH Antifungal and antibacterial activity of microalgae collected from paddy field of Iran: characterization of antimicrobial activity of *Chroococcus disperses*. Journal of Biological Sciences 2007; 7(6): 904-910.
19. Rao M, Malhotra S, Fatma T, Rattan A. Antimycobacterial activity from cyanobacterial extracts and phytochemical screening of methanol extract of Hapalosiphon. Pharmaceutical Biology 2007;45: 88-93
20. Drobac-Åik AV, Duliã TI, Stojanoviã DB, Sviråev ZB The importance of extremophile cyanobacteria in the production of biological active compounds. Matica Srpska Proceed. Natural Science Novi Sad 2007;112: 57—66.
21. Pawar ST, Puranik PR. Screening of terrestrial and freshwater halotolerant cyanobacteria from antifungal activities. World J Biotechnol 2008; 24: 1019-1025.
22. Meizoso R, Jaime L, Santoyo S, Cifuentes A, Reina GG-B, Senorans FJ, Ibanez E. Pressurized Fluid Extraction of Bioactive Compounds from *Phormidium* Species. Journal of Agricultural Food Chemistry 2008; 56: 3517–3523.
23. Dobretsov S, Abed RMM, Al-Maskari SMS, Al-Sabahi JN, Victor R. Cyanobacterial mats from hot springs produce antimicrobial compounds and quorum-sensing inhibitors under natural conditions. Journal of Applied Phycology 2011; 23: 983–993.
24. Madhumathi V, Deepa P, Jeyachandran S, Manoharan C, Vijayakumar S Antimicrobial Activity of Cyanobacteria Isolated from Freshwater Lake. International Journal of Microbiological Research 2011; 2 (3): 213-216.
25. Silva-Stenico ME, Silva CSP, Lorenzi AS, Shishido TK, Etchegaray A, Lira SP, Moraes LAB, Fiore MF. Non-ribosomal peptides produced by Brazilian cyanobacterial isolates with antimicrobial activity. Micorbiological Research 2011;166: 161-175.
26. Prabakaran M. Invitro antimicrobial potentials of marine *Oscillatoria* species. Asian Journal of Plant Science Research 2011;1 (3): 58-64
27. Ramamurthy V, Raveendran S, Thirumeni S, Krishnaveni S. Antimicrobial activity of Heterocytic Cyanobacteria. International Journal of Advance Life Science 2012; 1: 32-39
28. Thummajitsakul S, Silprasit K, Sittipraneed S. Antibacterial activity of crude extracts of cyanobacteria Phormidium and Microcoleus species. African Journal of Microbiological Research 2012; 6(10): 2574-2579.
29. Balunas MJ, Linington RG, Tidgewell K, Fenner AM, Ureña LD, Togna GD, Kyle DE, Gerwick WH. Dragonamide E, a modified linear lipopeptide from Lyngbya majuscula with

antileishmanial activity. Journal of Natural Product 2010; 73: 60-66.
30. Nunnery JK, Mevers E, Gerwick WH. Biologically active secondary metabolites from marine Cyanobacteria. Current Opinion in Biotechnology 2010; 21: 787–793.
31. Harada K. Production of Secondary Metabolites by Freshwater Cyanobacteria. Chemical Pharmacology Bulletin 2004; 52(8): 889-899.
32. Sanchez LM, Lopez D, Vesely BA, Della Togna G, Gerwick WH, Kyle DE, Linington RG. Almiramides A-C: discovery and development of a new class of leishmaniasis lead compounds. Journal of Medicinal Chemistry 2010; 53: 4187-4197.
33. Mo S, Krunic A, Chlipala G, Orjala J. Antimicrobial Ambiguine Isonitriles from the Cyanobacterium Fischerella ambigua. Journal of Natural Product 2009; 72: 894–899.
34. Matern U, Oberer L, Erhard M, Herdman M, Weckesser J. Hofmannolin, a cyanopeptolin from *Scytonema hofmanni* PCC 7110. Phytochemistry 2003; 64: 1061–1067.
35. Zainuddin EN, Jansen R, Nimtz M, Wray V, Preisitsch M, Lalk M, Mundt S. Lyngbyazothrins A-D, Antimicrobial Cyclic Undecapeptides from the Cultured Cyanobacterium *Lyngbya* sp. Journal of Natural Product 2009; 72: 1373–1378.
36. Wright AD, Papendorf O, Ko¨nig GM. Ambigol C and 2,4-Dichlorobenzoic Acid, Natural Products Produced by the Terrestrial Cyanobacterium *Fischerella ambigua*. Journal of Natural Product 2005; 68: 459-461.
37. Ploutno A, Carmeli S. Nostocyclyne A, a Novel Antimicrobial Cyclophane from the Cyanobacterium *Nostoc* sp. Journal of Natural Product 2000; 63: 1524-1526.
38. Simmons TL, Engene N, Uren˜a LD, Romero LI, Ortega-Barrı´a E, Gerwick L, Gerwick WH. Viridamides A and B, Lipodepsipeptides with Antiprotozoal Activity from the Marine Cyanobacterium *Oscillatoria* nigro-Wiridis. Journal of Natural Product 2008; 71: 1544–1550.
39. Linington RG, Gonza´lez J, Uren˜a L, Romero LI, Ortega-Barrı´a E, Gerwick WH. Venturamides A and B: Antimalarial Constituents of the Panamanian Marine Cyanobacterium *Oscillatoria* sp. Journal of Natural Product 2007; 70: 397-401.
40. MacMillan JB, Ernst-Russell MA, Jeffrey S, de Ropp, Molinski TF. Lobocyclamides A-C, Lipopeptides from a Cryptic Cyanobacterial Mat Containing *Lyngbya confervoides*. Journal of Organic Chemistry 2002; 67: 8210-8215.
41. Biondi N, Piccardi R, Margheri MC, Rodolfi L, Smith GD, Tredici MR Evaluation of Nostoc strain ATCC 53789 as a potential source of natural pesticides. Applied Environmental Microbiology 2004; 70: 3313–3320.
42. Gutiérrez RMP, Flores AM, Solı´s RV, Jimenez JC. Two new antibacterial norabietane diterpenoids from cyanobacteria, Microcoleous lacustris. Journal of Natural Medicine 2008; 62: 328–331.
43. Kim H, Lantvit D, Hwang CH, Kroll DJ, Swanson SM, Franzblau SG, Orjala J. Indole alkaloids from two cultured cyanobacteria, *Westiellopsis* sp. and *Fischerella muscicola*, Bioorganic Medicinal Chemistry 2012; 20: 5290–5295.
44. Volk RB, Girreserb U, Al-Refaic M, Laatsch H. Bromoanaindolone, a novel antimicrobial exometabolite from the cyanobacterium *Anabaena constricta.* Natural Product Research 2009;23(7): 607–612.
45. Volk RB, Mundt S. Cytotoxic and non-cytotoxic exometabolites of the cyanobacterium Nostoc insulare. Journal of Applied Phycology 2007; 19: 55-62.
46. Volk RB, Furkert FH. Antialgal, antibacterial and antifungal activity of two metabolites produced and excreted by cyanobacteria during growth. Microbiological Research 2006; 161: 180-186.
47. Sudo H, Grant Burgess J, Takemasa H, Nakamura N, Matsunaga T. Sulfated exopolysaccharide production by the halophilic cyanobacterium *Aphanocapsa halophytica*. Current Microbiology 1995; 30: 219-222.
48. Falch BS, König GM, Wright AD, Sticher O, Angerhofer CK, Pezzuto JM, Bachmann H Biological activities of cyanobacteria: evaluation of extract and pure compounds. Plant Medicine 1995; 61: 321-328.
49. Jaki B, Orjala J, Sticher O. A novel extracellular diterpenoid with antibacterial activity from the cyanobacterium *Nostoc commune*. Journal of Natural Product 1999; 62: 502–503.
50. Stratmann K, Moore RE, Bonjouklian R, Deeter JB, Patterson GML, Shaffer S, Smith CD, Smitka TA. Welwitindolinones, unusual alkaloids from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata* Relationship to fischerindoles and hapalindoles. Journal of American Chemical Society 1994; 116: 9935-9942.
51. Hemscheidt T, Puglisi MP, Larsen LK, Petterson GML, Moore RE, Rios JL, Clardy J. Structure and biosynthesis of borophycin, a new boeseken complex of boric acid from marine strain of the blue-green alga *Nostoc linckia*. Journal of Organic Chemistry 1994; 59: 3467-3471.
52. Borowitzka MA. Microalgae as sources of pharmaceuticals and other biologically active compounds. Journal of Applied Phycology 1995; 7: 3-15.
53. Runnegar M, Berndt N, Kong SM, Lee EY, Zhang L. In vivo and in vitro binding of microcystin to protein phosphatases 1 and 2A. Biochemistry Biophysics Research Community 1995; 216: 162-169.
54. Orjala J, Gerwick WH. Barbamide, a Chlorinated Metabolite with Molluscicidal Activity from the Caribbean Cyanobacterium *Lyngbya majuscule*. Journal of Natural Product 1996; 59: 427-430.
55. Boyd MR, Gustafson KR, McMohan JB, Shoemaker RH, O'Keefe BR, Mori T, Gulakowski RJ, Wu L, Rivera MI, Laurencot CM, Currens MJ, Cardellina IJH, Buckheit JRW, Nara PL, Pannell LK, Sowder IRC, Henderson LE Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: potential application to microbicide development. Antimicrobial Agent Chemotherapy 1997; 41: 1521-1530.
56. Sano T, He J, Liu Y, Kaya K. Isolation of bioactive compounds in cyanobacteria from Chinese fresh water: 1. Trypsin inhibitor. Physiological Research 1998; 46: 13-17.
57. Singh IP, Milligan KE, Gerwick WH. Tanikolide, a Toxic and Antifungal Lactone from the Marine Cyanobacterium *Lyngbya majuscule*. Journal of Natural Product 1999; 62: 1333-1335.
58. Hirata K, Takashina J, Nakagami H, Ueyama S, Murakami K, Kanamori T, Miyamoto K. Growth inhibition of various organisms by a violet pigment, nostocine A, produced by *Nostoc spongiaeforme*. Bioscience Biotechnology Biochemistry 1996; 66: 1905–1906.
59. Becher PG, Beuchat J, Gademann K, Jüttner F Nostocarboline: isolation and synthesis of a new cholinesterase inhibitor from Nostoc 78-12A. Journal of Natural Product 2005; 68: 1793-1795.
60. Zheng CJ, Yoo J-S, Lee T-G, Cho H-Y, Kim Y-H, Kim W-G. Fatty acid synthesis is a target for antibacterial activity of unsaturated fatty acids. FEBS Letter 2005; 579: 5157-5162.
61. Zelík P, Lukesová A, Voloshko LN, Stys D, Kopecký J. Screening for acetylcholinesterase inhibitory activity in cyanobacteria of the genus *Nostoc*. Journal of Enzyme Inhibition Medicinal Chemistry 2009; 24(2): 531-536.
62. Choi H, Oh SK, Yih W, Chin J, Kang H, Rho JR (2008) Cyanopeptoline CB071: a cyclic depsipeptide isolated from the freshwater cyanobacterium *Aphanocapsa* sp. Chem Pharm Bull (Tokyo) 56: 1191-1193.
63. Rodríguez-Meizoso I, Jaime L, Santoyo S, Cifuentes A, García-Blairsy Reina G, Señoráns FJ, Ibáñez E. Pressurized fluid extraction of bioactive compounds from Phormidium species. Journal of Agricultural Food Chemistry 2008;28;56(10): 3517-3523 .
64. Kwan JC, Rocca JR, Abboud KA, Paul VJ, Luesch H. Total Structure Determination of Grassypeptolide, a New Marine Cyanobacterial Cytotoxin. Organic Letter 2008; 10 (5): 789-792.
65. Teruya T, Sasaki H, Fukazawa H, Suenaga K. Bisebromamide, a potent cytotoxic peptide from the marine cyanobacterium Lyngbya sp.: isolation, stereostructure, and biological activity. Organic Letter 2009; 11: 5062-5065.
66. Balunas MJ, Grosso MF, Villa FA, Engene N, McPhail KL, Tidgewell K, Pineda LM, Gerwick L, Spadafora C, Kyle DE,

Gerwick WH. Coibacins A_D, Antileishmanial Marine Cyanobacterial Polyketides with Intriguing Biosynthetic Origins. Org Lett 2012; 14: 3878- 3881.

67. Kang H, Santarsiero BD, Kim H, Krunic A, Shen Q, Swanson SM, Chai H, Kinghorn AD, Orjala J. Merocyclophanes A and B, antiproliferative cyclophanes from the cultured terrestrial Cyanobacterium Nostoc sp. Phytochemistry 2012; 79: 109–115.