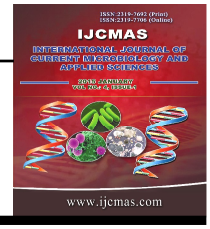
International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 4 Number 1 (2015) pp. 310-317**
http://www.ijcmas.com



Review Article

Cyanobacterial natural products as antimicrobial agents

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A B S T R A C T

K e y w o r d s

Cyanobacteria, Natural products, Bioactive compounds, Pharmaceutical compounds, Antimicrobial

Cyanobacteria (blue-green algae) constitute a morphologically diverse and widely distributed group of Gram-negative photosynthetic prokaryotes. Possessing tremendous adaptability to varying environmental conditions, effective protective mechanisms against various abiotic stresses and metabolic versatility, they colonize and grow in different types of terrestrial and aquatic habitats. In addition to the potential applications of cyanobacteria in various fields, such as agriculture, aquaculture, pollution control, bioenergy and nutraceuticals, they produce chemically diverse and pharmacologically important novel bioactive compounds, including antimicrobial compounds (antibacterial, antifungal and antiviral). The emergence and spread of antibiotic resistance in pathogenic microbes against commonly used antibiotics necessitated the search for new antimicrobial agents from sources other than the traditional microbial sources (streptomycetes and fungi). Various features of cyanobacteria, including their capability of producing antimicrobial compounds, make them suitable candidates for their exploitation as a natural source of antimicrobial agents.

Introduction

Cyanobacteria (Blue-green algae) are a primitive, diverse and ubiquitous group of photosynthetic prokaryotes, exhibiting resemblance with Gram-negative bacteria in cellular organization and green plants in oxygenic photosynthesis (Stanier and Cohen-Bazire, 1977). With long evolutionary history, they are among the oldest life forms existing on earth. They colonize, grow and survive in almost all kinds of terrestrial and aquatic (freshwater and marine) ecosystems which can be attributed to their tremendous adaptability to varying environmental conditions as well as effective protective and tolerance mechanisms against various abiotic stresses (Tandeau de Marsac and Houmard, 1993; Potts, 1999; Ehling-Schulz and Scherer, 1999). With remarkable diversity in their structure, which may be unicellular, colonial or filamentous (branched or unbranched); they include 150 genera with more than 2000 species. The presence or production of a wide array of photosynthetic pigments, storage products, and primary and secondary metabolites indicates their biochemical diversity. They are considered as metabolically versatile organisms as well as highly productive and efficient biological systems. Both ecologically and economically, they are important organisms with varied implications and applications. In addition to the potential applications of cyanobacteria in various fields, such as agriculture, aquaculture, human nutrition or nutraceuticals, bioenergy and pollution control (bioremediation), they are known to produce a bewildering array of novel bioactive compounds with diverse activities. Bioactive (biologically active compounds) are the compounds/molecules which at low concentrations affect a living organism, tissue or cell in beneficial or detrimental manner or may elicit pharmacological or toxicological effects in humans and animals. They may be synthetic or natural, produced by various species microbes and plants. Most of them are secondary metabolites with diverse chemical structures. Among the known cyanobacterial bioactive compounds, many are pharmacologically important and hold immense potential for drug development. These include antimicrobial compounds, anticancerous/antineoplastic agents, antimitotic agents, muscle-relaxants, immunomodulatory agents and enzyme inhibitors (Singh *et al*., 2005; Singh *et al*., 2011; Prasanna, 2010; Volk and Fulkert, 2006; Tan, 2007; Skulberg, 2000; Barrios-Llerena, 2007; Patterson *et al*., 1994). Bioactive compounds produced by cyanobacteria may be released outside the cells, either actively or passively or by autolysis (Metting and Pyne, 1986).

Antimicrobial compounds

Antimicrobial properties of natural products from different sources have gained importance in view of the emergence and spread of antibiotic resistance in pathogenic microbes, which constitutes a major and challenging public health problem, due to indiscriminate use or misuse of antibiotics (Trias and Gordon, 1997; Cowan, 1999). Organisms other than cyanobacteria, such as streptomycetes and fungi are the source of majority of antibiotics. Photoautotrophic organisms like cyanobacteria have not yet received much attention as a source of antibiotics or antimicrobial compounds. However, systematic screening and phytochemical investigation of cyanobacteria over the past two decades have revealed the production of antimicrobial compounds (e.g. antibacterial, antifungal, antiviral) by many species. Some antimicrobial compounds are known to exhibit single activity while others exhibit multiple activities. The biosynthetic pathways responsible for the production of various cyanobacterial antimicrobial compounds and the factors regulating their production are not completely known. However, certain reports indicate that the production of antimicrobial compounds in cyanobacteria is regulated by culture conditions and nutrients (Fish and Codd, 1994; Patterson and Bolis, 1993, 1995).

Antibacterial and antifungal agents

Cyanobacteria of genera *Scytonema* and *Tolypothrix* produce potent antifungal and cytotoxic agents, called scytophycins, which are chemically congeneric macrolides (Ishibashi *et al*., 1986; Carmeli *et al*., 1990). Tolytoxin (6-hydroxy-7-0-methyl-scytophycin b), a well characterized scytophycin, was originally isolated from the cyanobacterium *Tolypothrix conglutinata* var. c*olorata* in 1977 (Moore, 1981). The cyanobacterial species producing scytophycins and tolytoxin include *Scytonema pseudohofmanni, S.mirabile, S. burmanicum* and *S. ocellatum* (Ishibashi *et al*., 1986; Carmeli *et al*., 1990). In addition to antifungal activity, scytophycins and tolytoxin exhibit strong cytotoxicity towards cancerous cell lines (Moore *et al*., 1986; Patterson and Carmeli, 1992).

Various cyclic peptides and depsipeptides isolated from cyanobacteria have been reported as antimicrobial agents. These include tenuecyclamides (antibacterial and cytotoxic agent) from lithophytic cyanobacterium *Nostoc spongiaeforme* var. *tenue* (Banker and Carmeli, 1998), schizotrin A (antifungal and antibacterial compound) from *Schizothrix* sp. (Pergament and Carmeli, 1994), hormothamnins (antibacterial and antifungal compounds) from the marine cyanobacterium *Hormothamnion enteromorphoides* (Gerwick *et al*., 1989), laxaphycins (antifungal agents) from the terrestrial cyanophyte *Anabaena laxa* (Frankmölle *et al*., 1992a,b), majusculamide C (antifungal agent) from the marine cyanobacterium *Lyngbya majuscula* (Carter *et al*., 1984), kawaguchipeptin B (antibacterial agent) from the toxic cyanobacterium *Microcystis aeruginosa* (Ishida *et al*., 1997), calophycin (fungicide) from the terrestrial blue-green alga *Calothrix fusca* (Moon *et al*., 1992), and tolybyssidins (antifungal compounds) from the epilithic cyanobacterium *Tolypothrix byssoidea* (Jaki *et al*., 2001).

The cyanobacterium *Nostoc commune* produces a novel antibacterial compound, called noscomin, which is a diterpenoid (Jaki *et al.*, 1999). Carbamidocyclophanes A-E (chlorinated paracyclophanes), exhibiting antibiotic and cytotoxic activity, has been isolated from the cyanobacterium *Nostoc* sp. (Bui *et al*., 2007).

Indole alkaloids, named as hapalindoles, are antibacterial and antifungal agents produced by an edaphic cyanobacterium *Hapalosiphon fontinalis* (Moore *et al*., 1987). The *Fischerella muscicola*, a terrestrial cyanobacterium, has been reported to produce an antifungal compound, fischerindole L, which is chemically related to hapalindoles (Park *et al*., 1992). Tubercidin and toyocamycin are fungicidal and cytotoxic nucleosides produced by *Plectonema radiosum* and *Tolypothrix tenuis*, respectively (Stewart *et al*., 1988). Ambiguine isonitriles, exhibiting fungicidal activity, are hapalindole-type alkaloids produced by cyanobacterial species *Fischerella ambigua*, *Hapalosiphon hibermicus* and *Westiellopsis prolifica* of the family Stigonemataceae (Smitka *et al*., 1992). The antifungal compounds tjipanazoles, which are chemically indolocarbazoles, have been isolated from the terrestrial cyanobacterium *Tolypothrix tjipanasensis* (Bonjouklian *et al*., 1991). Ambigols (polychlorinated aromatic compounds), exhibiting antibacterial and antifungal activities, are produced by the terrestrial cyanobacterium *Fischerella ambigua* (Falch *et al*., 1993).

The antibacterial oxazole peptide alkaloid, named as muscoride A, is produced by the fresh water cyanobacterium *Nostoc muscorum* (Nagatsu *et al*., 1995). Malyngamides, amides of the fatty acid (&) -7(S)-methoxytetradec-4(E)-enoate, are antibacterial agents isolated from the marine cyanobacterium *Lyngbya majuscula* (Gerwick *et al*., 1987). Tanikolide, an antifungal lactone, is another antimicrobial compound isolated from *L. majuscula* (Singh *et al*., 1999).

Antiviral agents

With the aim of discovering new antiviral agents, extracts of various cyanobacterial species were screened against human pathogenic viruses, including HIV (Knübel *et al*., 1990; Gustafson *et al*., 1989). The sulfoglycolipids isolated from cyanobacteria have been reported to inhibit the activity of reverse transcriptase of human immunodeficiency virus (HIV) (Loya *et al*., 1998). Cyanovirin-N, a carbohydrate binding protein, isolated from the cyanobacterium *Nostoc ellipsosporum*, exhibits potent anti-HIV activity (Boyd *et al*., 1997; Botos and Wlodawer, 2003). It binds to viral surface envelope glycoprotein gp120, interfering with the fusion of HIV with the cellular receptor CD4. Bokesch *et al.* (2003) isolated a potent novel anti-HIV protein, scytovirin, from aqueous extracts of the cultured cyanobacterium *Scytonema varium* that acts by binding to viral coat proteins gp120, gp160 and gp41 (Bokesch *et al*., 2003). The terrestrial cyanobacterium *Nostoc flagelliforme* is known to produce an antiviral acidic polysaccharide, nostoflan, exhibiting potent activity against HSV-1 (herpes simplex virus type-1), HSV-2, human cytomegalovirus and influenza A virus (Kanekiyo *et al*., 2005, 2007, Hayashi *et al*., 2008). Cyclic depsipeptides, ichthyopeptins A and B, isolated from the cyanobacterium *Microcystis ichthyoblabe*, possess antiviral activity against influenza A virus (Zainuddin *et al*., 2007). Calcium spirulan (Ca-SP), a natural sulfated polysaccharide, isolated from *Spirulina platensis*, has been reported to exhibit antiviral activity against various enveloped viruses, such as human immunodeficiency virus type-1 (HIV-1), herpes simplex virus type-1 (HSV-1), measles virus, mumps virus, influenza A virus and human cytomegalovirus (Hayashi *et al*., 1996a,b). Ca-SP selectively inhibits the penetration of virus into host cells.

Cyanobacteria have been recognized as a promising and prodigious source of novel pharmaceutical compounds of various types. The development of resistance in pathogenic microorganisms against commonly used antibiotics made imperative to look for new antimicrobial agents from natural sources other than the traditional microorganisms. Interestingly, the production of antimicrobial compounds by various species of cyanobacteria opens up new possibilities for the exploitation of these organisms as potential source of antimicrobial agents or antibiotics. The desired features, such as rapid growth rate, simple growth requirements, and amenability to controlled laboratory culture, ubiquity and easy accessibility make cyanobacteria suitable candidates for their use and exploitation as a natural source of antimicrobial agents and other pharmaceutical compounds. Additionally, because of their antimicrobial compounds/activities, they would be suitable biocontrol agents for phytopathogenic bacteria and fungi. The potential of cyanobacteria in pharmaceuticals has yet to be fully realized. Increased research efforts towards extensive screening, purification and characterization of antimicrobial compounds, strain improvement, genetic manipulation, metabolic engineering, optimization of growth media and culture conditions, and high density culture are needed. Ecologically, the production of antimicrobial compounds by cyanobacteria is important because of their possible role in chemical interactions that occur in microbial communities in nature. They may confer selective advantage to cyanobacteria to grow and survive in natural habitats.

References

Banker, R., Carmeli, S. 1998. Tenuecyclamides A-D, cyclic hexapeptides from the cyanobacterium *Nostoc spongiaeforme* var. *tenue*. *J. Nat. Prod.*, 61: 1248–1251.

Barrios–Llerena, M. E., Burja, A.M., Wright, P.C. 2007. Genetic analysis of polyketide synthase and peptide synthetase genes in cyanobacteria as a mining tool for secondary metabolites. *J. Ind. Microbiol. Biotechnol.*, 34: 443–456.

Bokesch, H.R., O'Keefe, B.R., McKee, T.C., Pannell, L.K., Patterson, G.M.L., Gardella, R.S., Sowder, R.C., Turpin, J., Watson, K., Jr. Buckheit, R.W., Boyd, M.R. 2003. A potent novel anti–HIV protein from the cultured cyanobacterium *Scytonema varium*. *Biochemistry,* 42(9): 2578–84.

Bonjouklian, R., Smitka, T.A., Doolin, L.E., Molloy, R.M., Debono, M., Shaffer, S.A., Moore, R.E., Stewart, J.B., Patterson, G.M.L. 1991. Tjipanazoles, new antifungal agents from the blue–green alga *Tolypothrix tjipanasensis*. *Tetrahedron,* 47: 7739–7750.

Botos, I., Wlodawer, A. 2003. Cyanovirin–N: a sugar–binding antiviral protein with a new twist. *CMLS Cell. Mol. Life Sci.*, 60: 277–287.

Boyd, M.R., et al. 1997. Discovery of cyanovirin–N, a novel human immunodeficiency virus–inactivating protein that binds viral surface envelope glycoprotein gp120: potential applications to microbicide development. *Antimicob. Agents Chemother.*, 41(7): 1521–1530.

Bui, T.N., Jansen, R., Pham, T.L., Mundt, S. 2007. Carbamidocyclophanes A–E, chlorinated paracyclophanes with cytotoxic and antibiotic activity from the Vietnamese cyanobacterium, *Nostoc* sp. *J. Nat. Prod.*, 70: 499–503.

Carmeli,S., Moore, R.E., Patterson, G.M.L. 1990. Tolytoxin and new scytophycins from three species of *Scytonema*. *J. Nat. Prod.,* 53: 1533–1542.

Carter, D.C., Moore, R.E., Mynderse, J.S., Niemczura, W.P., Todd, J.S. 1984. Structure of majusculamide C, a cyclic depsipeptide from *Lyngbya majuscula*. *J. Org. Chem.,* 49: 236–241.

Cowan, M.M. 1999. Plant products as antimicrobial agents. *Clin. Microbiol. Rev.*, 12: 564–582.

Ehling–Schulz, M., Scherer, S. 1999. UV protection in Cyanobacteria. *Eur. J. Phycol.,* 34: 329–338.

Falch, B.S., König, G.M., Wright, A.D., Sticher, O., Rüegger, H., Bernardinelli, G. 1993. Ambigol A and B: new biologically active polychlorinated aromatic compounds from the terrestrial blue–green alga *Fischeralla ambigua*. *J. Org. Chem.*, 58: 6570–6575.

Fish, S.A., Codd, G.A. 1994. Analysis of culture conditions controlling the yield of bioactive material produced by the thermotolerant cyanobacterium (blue–green alga) *Phormidium*. *Eur. J. Phycol.*, 29: 261–266.

Frankmölle, W.P., Knübel, G., Moore, R.E., Patterson, G.M.L. 1992b. Antifungal cyclic peptides from the terrestrial blue–green agla *Anabaena* *laxa*. II. Structures of laxaphycins A,B,D and E. *J. Antibiotics,* 45: 1458–1466.

Frankmölle, W.P., Larsen, L.K., Caplan, F.R., Patterson, G.M.L., Knübel, G., Levine, I.A., Moore, R.E. 1992a. Antifungal cyclic peptides from the terrestrial blue–green agla *Anabaena laxa*. I. Isolation and biological properties. *J. Antibiotics,* 45: 1451–1457.

Gerwick, W.H., Mrozek, Moghaddam, Ch., Agarwal, S.K. 1989. Novel cytotoxic peptides from the tropical marine cyanobacterium *Hormothamnion enteromorphoides*. I. Discovery, isolation and initial chemical and biological characterization of the hormothamnins from wild and cultured material. *Experientia*, 45: 115–121.

Gerwick,W.H., Reyes, S., Alvarado, B. 1987. Two malyngamides from the Carribean cyanobacterium *Lyngbya majuscula*. *Phytochemistry*, 26: 1701–1704.

Gustafson, K.R., Cardellina II, J.H., Fuller, R.W., Weislow, O.S., Kiser, R.F., Snader, K.M., Patterson, G.M.L., Boyd, M.R. 1989. AIDS – antiviral sulfolipids from cyanobacteria (blue–green algae). *J. Nat. Cancer Inst.,* 81: 1254–1258.

Hayashi, K., Kanekiyo, K., Ohta, Y., Lee, J.B., Takenaka, H., Hayashi, T. 2008. Anti–influenza A virus activity of an acidic polysaccharide from a blue–green alga *Nostoc flagelliforme*. *Planta Med.,*. 74: PA34.

Hayashi, K., Hayashi, T., Kojima, I. 1996a. A natural sulfated polysaccharide, calcium spirulan, isolated from *Spirulina platensis*: in vitro and ex vivo evaluation of anti–herpes simplex virus and anti–human immunodeficiency virus activities. *AIDS Res. Hum. Retroviruses,* 12(15): 1463–1471.

Hayashi, T., Hayashi, K., Maeda, M., Kojima, I. 1996b. Calcium spirulan, an inhibitor of enveloped virus replication, from a blue–green alga *Spirulina platensis*. *J. Nat Prod.,* 59(1): 83–87.

Ishibashi, M., Moore, R.E., Patterson, G.M.L., Xu, C., Clardy, J. 1986. Scytophycins, cytotoxic and antimycotic agents from the cyanophyte *Scytonema pseudohofmanni*. *J. Org. Chem.,* 51: 5300–5306.

Ishida, K., Matsuda, H., Murakami, M., Yamaguchi, K. 1997. Kawaguchipeptin B, an antibacterial cyclic undecapeptide from the cyanobacterium *Microcystis aeruginosa*. *J. Nat. Prod.,* 60: 724–726.

Jaki, B., Orjala, J., Sticher, O. 1999. A novel extracellular diterpenoid with antibacterial activity from the cyanobacterium *Nostoc commune*. *J. Nat. Prod.,* 62: 502–503.

Jaki, B., Zerbe, O., Heilmann, J., Sticher, O. 2001. Two novel cyclic peptides with antifungal activity from the cyanobacterium *Tolypothrix byssoidea* (EAWAG 195). *J. Nat. Prod.,* 64: 154–158.

Kanekiyo, K., Hayashi, K., Takenaka, H., Lee, J–B., Hayashi, T. 2007. Anti–herpes simplex virus target of an acidic polysaccharide, Nostoflan, from the edible blue–green alga *Nostoc flagelliforme*. *Biol. Pharm. Bull.,* 30(8): 1573–1575.

Kanekiyo, K., Lee, J.B., Hayashi, K., Takenaka, H., Hayakawa, Y., Endo, S., Hayashi, T. 2005. Isolation of an antiviral polysaccharide, nostoflan, from a terrestrial cyanobacterium, *Nostoc flagelliforme*. *J. Nat. Prod.*, 68(7): 1037–1041.

Knübel,G., Larsen, L.K., Moore, R.E., Levine, I.A., Patterson, G.M.L. 1990. Cytotoxic, antiviral indolocarbazoles from a blue–green alga belonging to the Nostocaceae. *J. Antibiotics*, 43: 1236–1239.

Loya, S., et al., 1998. The inhibition of reverse transcriptase of HIV–1 by the natural sulfoglycolipids from cyanobacteria: contribution of different moieties to their high potency. *J. Nat. Prod.*, 61: 891–895.

Metting, B., Pyne, J.W. 1986. Biologically active compounds from microalgae. *Enzyme Microb. Technol.*, 8: 386–394.

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

Moore, R.E. 1981. Constituents of blue–green algae. In: Scheuer, P.J. (Ed.), Marine natural products, Vol. 4. Academic Press, New York. Pp. 1–52.

Moore, R.E., Cheuk, C., Yang, X–Q.G., Patterson, G.M.L., Bonjouklian, R., Smitka, T.A., Mynderse, J.S., Foster, R.S., Jones, N.D., Swartzendruber, J.K., Deeter, J.B. 1987. Hapalindoles, antibacterial and antimycotic alkaloids from the cyanophyte *Hapalosiphon fontinalis*. *J. Org. Chem.*, 52: 1036–1043.

Moore, R.E., Patterson, G.M.L., Mynderse, J.S., Jr. Barchi, J.J., Norton, T.R., Furusawa, E., Furusawa, S. 1986. Toxins from cyanophytes belonging to the Scytonemataceae. *Pure Appl. Chem.* 58: 263–271.

Nagatsu, A., Kajitani, H., Sakakibara, J. 1995. Muscoride A: a new oxazole peptide alkaloid from freshwater cyanobacterium *Nostoc muscorum*. *Tetrahedron Lett.*, 36: 4097–4100.

Park, A., Moore, R.E., Patterson, G.M.L. 1992. Fischerindole L, a new isonitrile from the terrestrial blue–green alga *Fischerella muscicola*. *Tetrahedron Lett.*, 33: 3257–3260.

Patterson, G.M.L., Bolis, C.M. 1993. Regulation of scytophycin accumulation in cultures of *Scytonema ocellatum*. I. Physical factors. *Appl. Microbiol. Biotechnol.*, 40: 375–381.

Patterson, G.M.L., Bolis, C.M. 1995. Regulation of scytophycin accumulation in cultures of *Scytonema ocellatum*. II. Nutrient requirements. *Appl. Microbiol. Biotechnol.*, 43: 692–700.

Patterson, G.M.L., Carmeli, S. 1992. Biological effects of tolytoxin (6–hydroxy–7–0–methyl–scytophycin b), a potent bioactive metabolite from cyanobacteria. *Arch. Microbiol.*, 157: 406–410.

Patterson, G.M.L., Larsen, L.K., Moore, R.E. 1994. Bioactive natural products from blue–green algae. *J. Appl. Phycol.*, 6: 151–157.

Pergament, I., Carmeli, S. 1994. Schizotrin A: a novel antimicrobial cyclic peptide from a cyanobacterium. *Tetrahedron Lett.*, 35: 8473–8476.

Potts, M. 1999. Mechanisms of desiccation tolerance in cyanobacteria. *Eur. J. Phycol.*, 34: 319–328.

Prasanna,R., Sood, A., Jaiswal, P., Nayak, S., Gupta, V., Chaudhary, V., Joshi, M., Natrajan, C. 2010. Rediscovering cyanobacteria as valuable sources of bioactive compounds (Review). *Appl.*

Bochem. Microbiol., 46(2): 119–134.

Singh, I.P., Milligan, K.E., Gerwick, W.H. 1999. Tanikolide, a toxic and antifungal lactone from the marine cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.,* 62: 1333–1335.

Singh, R.K., Tiwari, S.P., Rai, A.K., Mohapatra, T.M. 2011. Cyanobacteria: an emerging source for drug discovery. *J. Antibiotics*, 64: 401–412.

Singh, S., Kate, B.N., Banerjee, U.C. 2005. Bioactive compounds from cyanobacteria and microalgae: an overview. *Crit. Rev. Biotechnol.,* 25(3): 73–95.

Skulberg, O.M. 2000. Microalgae as a source of bioactive molecules– experience from cyanophyte research. *J. Appl. Phycol.,* 12: 341–348.

Smitka, T.A., Bonjouklian, R., Doolin, L., Jones, N.D., Deeter, J.B., Yoshida, W.Y., Prinsep, M.R., Moore, R.E., Patterson, G.M.L. 1992. Ambiguine isonitriles, fungicidal hapalindole–type alkaloids from three genera of blue–green algae belonging to the Stigonemataceae . *J. Org. Chem.,* 57: 857–861.

Stanier, R.Y., Cohen–Bazire, G. 1977. Phototrophic prokaryotes: the cyanobacteria. *Ann. Rev. Microbiol.,* 31: 225–274.

Stewart, J.B., Bornemann, V., Chen, J.L., Moore, R.E., Caplan, F.R., Karuso, H., Larsen, L.K., Patterson, G.M.L. 1988. Cytotoxic, fungicidal nucleosides from blue–green algae belonging to the Scytonemataceae. *J. Antibiotics*, 41: 1048–1056.

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

Tandeau de Marsac, N., Houmard, J. 1993. Adaptation of cyanobacteria to environmental stimuli: new steps towards molecular mechanisms. *FEMS Microbiol. Rev.,* 104: 119–190.

Trias, J., Gordon, E.M. 1997. Innovative approaches to novel antibacterial drug discovery. *Curr. Opin. Biotech.,* 8: 757–762.

Volk, R.B., Fulkert, F. 2006. Antialgal, antibacterial and antifungal activity of two metabolites produced by cyanobacteria during growth. *Microbiol. Res.,* 161: 180–186.

Zainuddin, E.N., Mentel, R., Wray, V., Jansen, R., Nimtz, M., Lalk, M., Mundt, S. 2007. Cyclic depsipeptides, ichthyopeptins A and B, from *Microcystis ichthyoblabe*. *J. Nat. Prod.,* 70(7): 1084–1088.