Chapter

Sub-Aerial Cyanobacteria: A Survey of Research with Antimicrobial Properties for Pharmaceutical Approaches

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Abstract

Cyanobacteria also known as Blue Green Algae (BGA) are widely distributed in environments. Cyanobacteria or BGA commonly being aquatic are also reported from terrestrial ecosystems like sub-aerial surface of temples, monuments and building facades etc., represent their versatile habitats and extremophilic nature. These organisms are the excellent material for primary and secondary metabolites has been investigated by ecologists, physiologists, biochemists and molecular biologists. Scientists and young researchers require knowledge of the potential cyanobacteria and their exploitation in order to formulate effective natural compound or drug remedies. A large number of reports in literature stress have acknowledged the use of Cyanobacteria in pharmaceutical and industries, due to the production of different secondary metabolites with diverse bioactivities. However, very less study is being carried out with respect to exploitation of these sub-aerial Cyanobacteria group for production of different secondary metabolites with biological activities. Since many cyanobacteria are also able to survive most type of stress/and or extreme, they may become even more important as antimicrobial agents of pharmaceuticals in the future. Hence, special attention is paid to these groups of organisms.

Keywords: sub-aerial cyanobacteria, extreme environment, antimicrobial agents, pharmaceutical sector

1. Introduction

The appearances of multi drug resistance among pathogens growing day by day. This could be attributable to prolonged and indiscriminate use of antibiotics and chemotherapeutic agents, over and/or under use of drugs, use of antibiotics without prior knowledge of antibiotic sensitivity pattern of the pathogens, non-completion of dose. In addition, prolonged use of antibiotics and chemotherapeutics results in many side effects too. So there has been a growing demand in search of some new source group of alternative antibiotics. Most of the academicians and researchers all over the world, starting from the ancient age, exploited medicinal and aromatic plants,

to a great extent for treatment of diseases and discovery of new antimicrobials or compounds with bioactivities. Based on the complexity in composition, extractions of compounds from microorganisms now are studies again for new antimicrobial compounds. A greater interest has been raised in the field of research towards bioactive compounds from algae. Secondary or primary metabolites of algae consist of diverse groups of chemical compounds. The antibiotic activity of algae has been reported since 1944 [1]. More than 164,784 algae species and infraspecific taxa are reported from all over the world in AlgaeBase whereas, regarding Cyanobacteria, 5152 species have been reported [2]. Among them few have been identified or tested for their efficiency. Algae are sources of amino acid, terpenoids, phlorotannins, steroids, phenolic compounds, halogenated ketones and alkanes and cyclic polysulphides [3]. The natural products from a wide variety of taxa have been isolated and tested for their potential biological activities [4]. Sub-aerial cyanobacteria are one of the important taxa of prokaryotic algae; distributed in extreme habitats need to be explored for their efficiency with respect to bioactivities, as prior research in this area has been inconclusive.

1.1 Cyanobacteria distribution in diverse habitats

Cyanobacteria (BGA) are gram negative photoautotrophic bacteria found in almost all ecological habitats, of aquatic and terrestrial origin. Aquatic forms are abundantly found in both marine and fresh water ecosystems including stagnant water bodies, under running water bodies, lagoons etc. Brackish water bodies also harbor a large number of Cyanobacterial species. Terrestrial habitats, including extreme environments also reflects the tolerance of Cyanobacteria have been reported as biofilms/ or crusts on the exposed surfaces of solid substrata in almost all climatic zones [5]. These organisms grow as epiphytes on tree bark, as epiliths on rocks and stones, and also on anthropogenic surfaces such as facades, concrete floors of roofs and other artificial surfaces of buildings where they cause esthetically unacceptable discolouration of the structures [6]. Such growths are common in humid places on uneven surfaces such as holes, crevices and also on damp building walls due to leaking, roof guttering, inadequate drainage of flat areas or from adjacent water courses. Their adaptation on surfaces of both modern and ancient buildings as well as old monuments represents them as sub-aerial Cyanobacteria/extremophiles since enduring extreme environments. They are particularly abundant in tropics as compared to temperate regions due to their capacity to resist very harsh conditions such as very high temperature, prolonged dry periods, extreme light intensity and UV radiation as they are the prolific producers of secondary metabolites, extracellular glycans, heat shock proteins and, UV pigments such as Mycosporine like amino acids (MAAs) and Scytonemins [7–9]. This population has been reported to have a characteristics appearance and develop a large number of photosynthetic pigments (chlorophyll, carotenoids and phycobiliproteins) including UV - absorbing compounds and pigments which play a key role in their protection and adaptability [10, 11]. These are certain attributes for their colonization and also have of great importance implications in scientific research and for human welfare.

According to literature stresses, the organisms those occur on such substrata mainly consists of coccoid forms of the order Chroococcales (*Chroococcidiopsis*, *Chroococcus*, *Gloeocapsa*, *Myxosarcina*), filamentous forms of the order Oscillatoriales (*Plectonema*, *Leptolyngbya*, *Lyngbya*, *Microcoleus*, *Oscillatoria*, *Phormidium*, *Pseudophormidium*, *Schizothrix*) and Nostocales (*Calothrix*, *Nostoc*, *Scytonema*,

Tolypothrix) etc. Several researchers have studied and reported this type of forms from almost all climatic zones. Examples are building facades in Greece [12], buildings in South Eastern, Spain [13–18], building in American countries [19], building facades in France [20, 21], stone monument and building facades in Italy [22–25], monuments in Portugal [26, 27], monuments in Slovakia [28, 29] and modern/old monuments, India [30–39]. In general, the knowledge on sub-aerial Cyanobacteria diversity colonizing building facades and their exploitation in different applications is still limited. To our knowledge, few reports have been published that deal specifically with the presence of secondary metabolites and pigments of sub-aerial Cyanobacteria and algae isolated from facades of buildings, on structural of cultural heritage and on rock surfaces of different monuments. No systematic scientific approach has been taken yet in India including other countries on this subject. A few research workers have worked on the microorganisms from facades of buildings, cultural heritages and monuments and other material in different parts of the globe [40]. However, no effective chemical or compound which can be employed as an antimicrobial agent from sub-aerial species in Pharmaceutical and Nutraceuticals industries has not yet been reported for which search is on.

2. Bioactive compounds from cyanobacteria

Literature stresses isolation and identification of Cyanobacteria from a diverse environment with bioactivities, but only few research has focused on a variety of bioactive compounds produced by Cyanobacteria after analysis of a great number of marines [41–43], freshwater [44–46], terrestrial [47, 48], and hot spring [49, 50]. Cyanobacterial natural products still seem to prevail followed at much lesser proportions by alkaloids, aromatic compounds, cyclic depsipeptides, cyclic peptides, cyclic peptide, cyclophane, fatty acids, linear peptides, lipopeptides, nucleosides, phenols, macrolides, polyketides, polyphenyl ethers, porphinoids and terpenoids [51]. These interesting and biochemically active compounds possess biological activity covering a wide range of antibacterial [52–55], antifungal [56], antialgal [56], antiviral [57], anticancer effectiveness [58–60], and immunosuppressive [61] activities. Some bioactive lead compound are bastadin, bis-x-butyrolactone, hapalindole, didehydromirazole, kawaguchipeptin B, muscoride, noscomin, nostocine A, scytophytin, and lipids [62] exhibited with antibacterial activity and, ambiguines, calothrixin, cyanobacterin, fischerindole A, hapalindole, hassallidin, phytoalexin, scytophycin, tjipanazole and *Y*-lactone [63, 64] with antifungal activity and few compound such as 4,4′-dihydroxybiphenyl, norhamane pyrido (3,4-*b*)indole, beta-glucan, bacteriocin, ambiguines, parsiguine, scytoscalarol, hapalindole [65] which have been reported to show antimicrobial activity. However, only few of them have been investigated in details [66, 67] are described under this subpoint 2.1. Some known bioactivities as per reported are listed below (**Table 1**). Thus, screening efforts aimed to identify antimicrobial agents in sub-aerial Cyanobacteria which might reveal promising compounds.

2.1 Bioactive compounds and its inhibitory activity with actions

Earlier reports indicate that bioactive compounds contradict synthetic drugs in their composition and their arrangement of radicals and atoms. However, their inhibitory activities are much more depends on the nature of interaction between donor and target organisms. They may inhibit growth or photosynthesis, kill the competitor or exclude

Cyanobacteria	Bioactive compound	Properties	Bioactivity	References
Order: Chroococcales *Microcystis aeruginosa*	Kawaguchipeptin B	It is an antibacterial cyclic undecapeptide	Antibacterial	[71]
Chrococcus turgidus	Beta-glucan	It is a group of beta-D-glucose polysaccharides, form a linear backbone with 1–3 β-glycosidic bonds	Antimicrobial	[94]
Order: Nostocales *Scytonema hofmanni* PCC7110	Scytophytin	It is a congeneric macrolide	Antibacterial	[63]
Anabaena sp. BIR JV1 and *Anabaena* sp. HAN7/1 KP701033	Hassallidin	It is a glycosylated lipopeptides, an esterified eight residue cyclic peptide bonded with a carbohydrate and fatty acid chain. It is composed of non proteingenic amino acids	Antifungal	[63]
Anabaena cf. cylindrica PH133 AJ293110 and *Anabaena* sp. HAN21/1 KP701032	Scytophycin	It is a congeneric macrolide	Antifungal	[63]
Nostoc sp. CENA 219 KP701037 and *Nostoc calcicula* 6sf Cale KP701034	Hassallidin	It is a cyclic glycosylated lipopeptides, contains structural variation of dihydroxy fatty acids and complex glycosylated pattern of monosaccharides	Antifungal	[63, 98]
Fischerella ambigua, *Haplosiphon hibernicus*	Ambiguines	It is isonitrile containing alkaloids	Antibacterial Antifungal	[72, 73]
Scytonema sp.	Scytoscalarol	It is a sesquiterpene	Antibacterial Antifungal	[74]
Tolypothrix sp.	Hassallidin	It is a Glycosylated lipopeptides, an esterified eight residue cyclic peptide bonded with a carbohydrate and fatty acid chain	Antifungal	[75]

Cyanobacteria	Bioactive compound	Properties	Bioactivity	References
Scytonema hofmanni	*Y* – Lactone	They are cyclic esters of hydroxycarboxylic acids, which contain 1-oxacycloalkan-2-one structure, or analogues having heteroatom replacing one or more carbon atoms of the ring	Antifungal	[76]
Scytonema mirabile	Didehydromirabazole	It is an alkaloid otherwise known as 4-methylthiazoline	Antibacterial	[77]
Anabaena basta	Bastadin	It is available in many forms but Bastadin 5 is the bioactive compound	Antibacterial	[78]
Anabaena variabilis	Bis - (x -butyrolactone)	It acts as an intermediate compound for the synthesis of other chemicals like methyl-2-pyrrolidone and as prodrug for gamma hydroxybutyric acid. Used as recreational drug for humans	Antibacterial	[79]
Tolypothrix tjipanasensis	Tjipanazole	It is compound having the pyrrolo [3, 4 - c] ring of indolo [2, 3 - a] carbazoles	Antifungal	[80]
Nostoc sp.	Muscoride	It is a peptide alkaloid possessing *N*-(2-methyl-3-buten- 2- yl) valine and two contiguous methyloxazoles	Antibacterial	[81]
Fischerella muscicola	Fischerellin A	It is an allelochemicals compound	Antibacterial Antifungal	[82]
Nostoc commune	Nostofungicidin	It is a novel lipopeptide fungicide and contains β-amino acid, 3-amino-6-hydroxy stearic acid	Antifungal	[83]
N. commune	Noscomin	It is a diterpenoid skeleton, 8 - [(5-carboxy-2 - hydroxy) benzyl]-2-hydroxy - 1, 1, 4a, 7, 8 –pentamethyl - 1, 2, 3, 4, 4a, 6, 7, 8, 8a, 9, 10, 10a dodecahydrophenanthrene	Antibacterial	[84]
Nostoc spongigaeforme TISTR 8169	Nostocine A	It is a violet color nitrogen rich alkaloid with rare heterocyclic structure.	Antibacterial	[85]

Cyanobacteria	Bioactive compound	Properties	Bioactivity	References
Fischerella muscicola	Fischerindole L	It is an isonitrile tetracyclic allelochemicals	Antibacterial Antifungal	[86, 88]
Fischerella ambigua	Parsiguine	It is a cyclic polymer, oxygenated ethylenic compound	Antibacterial Antifungal	[87]
Scytonema ocellatum	Scytophycin	It is a phenolic compound, macrolide polyketides	Antibacterial Antifungal	[89]
Scytonema pseudohofmanni	Scytophytin	It is a congeneric macrolide	Antibacterial	[90]
Scytonema hofmanni	Cyanobacterin	It is a phenolic compound	Antifungal	[91]
Nostoc sp.	Cyanobacterin LU-1 and LU- 2	It contains a nitrous heterocycle with sugar and phenolic substituents	Antifungal	[92]
Calothrix sp.	Calothrixine A	It is an alkaloid compound	Antifungal	[92]
Fischerella sp.	12-epi-Hapalindole E isonitrile	These are polycyclic bioactive compounds	Antifungal	[92]
Fischerella sp.	Hapalindole	It is polycyclic, isothiocyanate bioactive compounds	Antibacterial	[93]
Nostoc CCC537	Hapalindole	It is a polycyclic ring bioactive compound	Antibacterial	[93]
Nostoc sp. 78–11 A-E	Bacteriocin	It is a proteinaceous or peptide toxins	Antimicrobial	[96]
Nostoc insulare 54.79	4,4′-dihydroxybiphenyl	It is a phenolic compound	Antibacterial Antifungal	[97]
Nodularia harveyana	Norhamane pyrido (3,4-*b*) indole	It is a prototype of β -carboline and nitrogen heterocycle	Antibacterial Antifungal	[97]
Anabaena oryza	Pentadecane	It is a constitution of diacetone alcohol and mesityl oxide as major components	Antibacterial Antifungal	[99]
Stigeonema ocellatum	(3E)-3-Icosene, (Z)-14-Tricosenyl formate, 6- Octen-1-ol 3,7-dimethyl- acetate and 9-Hexadecenoic acid octadecyl ester	It is a constitution of diacetone alcohol, mesityl oxide and heptadecane as major components	Antibacterial Antifungal	[99]

Cyanobacteria	Bioactive compound	Properties	Bioactivity	References
Order: Oscillatoriales *Oscillatoria* sp.	m-Xylene, 2,6,10,14-Tetramethylheptadecane, 2-Ethoxy2-methylbutane, propanedioic acid dimethyl ester, hexaethylene glycol dimethyl ether, propylene glycol trimer 3 and phthalic acid mono-(2-ethylhexyl) ester	It is a constitution of diacetone alcohol, acetic acid butyl ester and mesityl oxide as major components	Antibacterial Antifungal	[99]
Synechococcus sp., strain GFB01	6-pentadecanol and octadecyl acetate	It is a volatiles organic compound	Antibacterial Antifungal	[100]

Table 1.
Bioactive molecules or compound produced by various cyanobacteria on database.

it from the donor vicinity, may be potent in inhibiting protein–protein interactions resulting in effective immune response, signal transduction; mitosis and ultimately apoptosis without causing much harm to living organisms [68, 69]. A large number of novel antimicrobial agents have been identified with antimicrobial, antibacterial and antifungal activities globally represented in (**Table 1**). However, few compounds like ambiguines, calothrixine A, cyanobacterin, fischerindole L, hapalindole, hassallidin, muscoride, noscomin, nostocine, phytoalexin, scytophycin, scytoscalorol and tjipanazole etc., either synthetized by ribosomal pathways or by non-ribosomal pathways [70] have attained importance for their antimicrobial activity in the field of pharmaceutical sector. Most of the cyanobacteria bioactive compound reported here are generally soluble in organic solvents and with low molecular weight. With respect to their mode of action, a relatively limited number of compounds have been studied or identified based on growth inhibition against target organisms. Kawaguchipeptin B, an antibacterial cyclic undecapeptide isolated from the cultured cyanobacterium *Microcystis aeruginosa* (NIES-88) showed antibacterial activity by growth inhibition towards gram positive bacterium *Staphylococcus aureus* at a concentration of 1 μg/mL (MIC) [71]. Ambiguines reported from *Fischerella ambigua* and *Haplosiphon hibernicus* was found to inhibit bacteria like *Mycobacterium tuberculosis* and *Bacillus anthracis*, and fungi such as *Aspergillus oryzae*, *Candida albicans*, *Penicillium notatum*, *Saccharomyces cerevisiae* and *Trichophyton mentagrophytes* [72–74]. Hassallidin reported with various types (hassallidin A, hassallidin B, hassallidin D, hassallidin 12, hassallidin 14 and hassallidin 15) from three different species, *Tolypothrix*, *Anabaena* strain (BIR JV1 and HAN7/1) and *Nostoc* strain (6sf Calc and CENA 219) showed as a potent antifungal agent against *Aspergillus fumigatus* and *C. albicans* [75] through inhibiting growth. Similarly, many other compounds such as gamma lactone from *Scytonema hofmanni* [76], didehydromirabazole from *Scytonema mirabile* [77], bastadin and Bis-x-butyrolactones from *Anabaena basta* and *A. variabilis* [78, 79], tjipanazole from *T. tjipanasensis* [80], muscoride from *Nostoc muscorum* [81], fischerellin A produced by *Fischerella muscicola* [82], nostofungicidin, noscomin and nostacine A from *Nostoc commune* and *Nostoc spongigaeforme* TISTR 8169 against *Bacillus cereus*, *Staphylococcus epidermidis* and *Escherichia coli* [83–85], fischerindole L and Parsiguine from *Fischerella muscicola* and *Fischerella ambigua* [86–88], and Scytophycins from *Scytonema pseudohofmanni*, *S. hofmanni* PCC7110, *Nostoc* sp. HAN11/1 and *Anabaena cf. cylindrica* (BIR JV1 and HAN7/1) [89, 90] are demonstrated with antibacterial /or antifungal activity based on growth inhibition but the type of target organisms and mode of action is unclear. However, few compounds have been shown to exhibit their mode of action through inhibition of photosystem - II, or enzyme or nucleic acid synthesis and/ or cellular paralysis. Phytoalexin from *Scytonema 0cellatum* exhibited inhibition of fungal enzymes and mycelial growth including cytoplasmic granulation, disorganization of the cellular contents and rupture of the plasma membrane of fungi like *Aspergillus oryzae*, *C. albicans*, *Penicillium notatum* and *S. cerevisiae* [89]. Cyanobacterin from *Scytonema hofmanni* and *Nostoc* sp., both found to inhibit the photosystem II-mediated photosynthetic electron transfer [91, 92]. Calothrixine A from *Calothrix* sp., as antifungal activity leads to growth inhibition because of RNA synthesis inhibition [92]. Two alkaloids, hapalindole a polycyclic isothiocyanate and 12-*epi*-hapalindole E isonitrile from *Fisherella* sp., and *Nostoc CCC537* have pointed to inhibition towards bacteria (*Bacillus subtilis*, *M. tuberculosis* H37Rv, *S. aureus* ATCC25923, *Salminella typhi* MTCC3216, *Pseudomonas aeruginosa* ATCC27853, *E. coli* ATCC25992 and *Enterobacter aerogenes* MTCC2822) and fungi (*C. albicans*) based on RNA polymerase, DNA and protein synthesis [92, 93]. β-glucans, a beta-D-glucose polysaccharides from *Chrococcus turgidis* exhibited phagocytic activity and resistance

towards *B. subtilis*, *E. coli*, *P. aeruginosa* and *S. aureus* and have shown chronic wound healing activity either directly or indirectly by modulating the activity of diverse cells and growth factors to reparative process [94, 95]. Bacteriocin, an antimicrobial protein/or peptide toxin isolated from *Nostoc* sp. 78–11 A-E found to be inhibits protein and its actions against bacteria and cyanobacteria [96]. Other bioactive molecules like 4–4′-dihydroxybiphenyl (*Nostoc insulare* 54, 79), Norhamane pyrido (3,4-b) indole (*Nodularia harveyana*), Pentadecane (*Anabaena oryzae*), 6-pentadecanol and octadecyl acetate (*Synechococcus* strain), m-Xylene, 2,6,10,14-Tetramethylheptadecane, 2-Ethoxy2-methylbutane, propanedioic acid dimethyl ester (*Oscillatora* sp.), hexaethylene glycol dimethyl ether, propylene glycol trimer 3 and phthalic acid mono-(2-ethylhexyl) ester, (3E)-3-Icosene, (Z)-14-Tricosenyl formate (*Stigonema ocellatum*), 6- Octen-1-ol 3,7-dimethyl- acetate and 9-Hexadecenoic acid octadecyl ester [97–100] are reported with activity, although the mode of that action is still unknown.

3. Bioactivity of sub-aerial cyanobacteria

Many sub-aerial Cyanobacteria are known to tolerate environmental extremes as they possess a great capacity for producing biologically active compounds. Researchers are in believe that more harsh and extreme conditions lead to a wider production of a diverse range of more or less, specific substances thus pointing towards these organisms as brilliant candidates for antimicrobial properties. A few numbers of sub-aerial cyanobacteria compounds are found to inhibit the target organisms, making them an attractive source of antimicrobial agents. Some known bioactivities from ten sub-aerial cyanobacteria as per reported are listed below (**Table 2**). The chloroform fraction of *Scytonema* br1 isolated from wall and Terrace, Konark Temple, Puri, Odisha showed significant anticyanobacterial activity against *Anabaena* BT2 and *Nostoc* pbr01 and antialgal activity against a green alga *Bracteacoccus* [55]. The lipids extract from *Toxopsis calypsus* and *Phormidium melanochroun* isolated from caves established good antibacterial activity against *Enterococcus faecium* (VRE), *Enterococcus faecalis* (ATCC) and *S. aureus* (MRSA) by disrupting cellular membranes [101]. Another study reported the chloroform extracts of *Scytonema hofman* isolated from building facades showed antibacterial activity against *E. coli*, followed by *Klebsiella pneumonia* and *P. aeruginosa*, *S. aureus* [102]. There is a report that acetone extract of sub-aerial species, *Scytonema ocellatum* isolated from sub-aerial habitats exhibits antibacterial activity towards *E. coli*, *B. subtilis* and *S. aureus* and GC analysis showed 98% and 95.6% purity antibiosis [103]. The sub-aerial Cyanobacteria *Anabaena* sp. (VBCCA 052002) as dominant species on terracotta monuments of Bishnupur showed highest antibacterial activity against *S. aureus*, *Salmonella typhimurium* and *E. coli* with a MIC value of 100 μg/ml against *S. aureus* and 150 μg/ml against *S. typhimurium* [104]. In another study reported three different type of bioactive compounds such as 2, 4-Bis (2-methyl-2-propanyl) phenol - phosphorous acid ($C_{42}H_{69}O_6P$:Mw- 700 g/mol) as phenolic, and other two compound Ergost-5-en-3-ol ($C_{28}H_{38}O_4$: Mw-704 g/mol) and 7, 11-dihydroxysolasodine ($C_{27}H_{43}NO_4$: Mw-413 g/mol) as steroidal alkaloid from three sub-aerial cyanobacteria species, *Tolypothrix rechingeri*, *Scytonema hyalinum* and *Scytonema ocellatum* respectively which exhibiting antimicrobial activity against *E. coli*, *P. aeruginosa*, *S. aureus*, *C. albicans* and *Epidermaphyton flocossum* etc. [105]. Out of ten, one of the sub-aerial cyanobacteria, *Fischerella* sp. (NCBI Accession number MN593556) reported with most potent active compound with R_f value 0.96 of acetone fraction showed complete growth inhibition against *E. coli* and moderate

Building materials	Cyanobacteria	Bioactive compounds	Properties	References
Terrace wall, Temple	*Scytonema* br1	—	Anticyanobacterial Antialgal	[55]
Rock (Cave)	*Toxopsis calypsus Phormidium melanochroun*	Lipid	It is constitutions of different class of lipids like glycolipids, sphingolipids, sterol lipids, glycerolipids etc.	[101]
Limewashed wall (Building)	*Scytonema hofman*	—	Antibacterial	[102]
Cement wall (Building)	*Scytonema ocellatum*	—	Antibacterial	[103]
Terracotta wall (Monument)	*Anabaena* sp. (VBCCA 052002)	—	Antibacterial	[104]
Stone carving (Temple)	*Tolypothrix rechingeri*	2, 4-Bis (2-methyl-2-propanyl) phenol - phosphorous acid	It is phenolic compound	[105]
Rock (Cave)	*Scytonema hyalinum*	Ergost-5-en-3-ol and 7	It is a steroidal alkaloid	[105]
Cement wall (Building)	*S. ocellatum*	11-dihydroxysolasodine	It is a steroidal alkaloid	[105]
Cement wall (Building)	*Fischerella* sp. (Accession Number -MN593556)	Pentaphenyl ferrocene carboxamide	It is a heterocyclic alkaloid	[106]

Table 2.
Bioactive molecules or compound produced by various sub-aerial cyanobacteria on database.

activity to *C. albicans*, was identified as, Iron (2+) amino (cyclopenta 2,4 diene-1-ylidine) methanolate 1,2,3,4,5-pentaphenycyclopenta-2.4, dien-1-ide (Pentaphenyl ferrocene carboxamide), $C_{41}H_{31}FeNO$: Mw-610 g/mol and was found to be non-toxic against cells lines of *Catla thymus macrophage* and osteoblast precursor cell line of *Mus musculus* up to 72 hours, with a concentration range of 0.875 - 4 mg/ml indicated their potentiality for development of new antimicrobial compounds [106].

4. Sub-aerial Cyanobacteria: as a source of antimicrobial compounds towards pharmaceutical approaches.

In modern research, a number of significant advancements have been made in Cyanobacterial pharmacologically active compounds from natural resources like marine, freshwater, and very few terrestrial etc., and has received ever increasing interest. A large number of antibiotic compounds, many with novel structures, have been isolated and characterized, but few compounds such as dolastatins, soblidotin, Tasidotin, cryptophycin, curacin D and micropeptins exhibited very interesting results and successfully reached Phase II and Phase III of clinical trials [107–111]. Isolation of these compounds

from cyanobacteria species like *Symploca* sp., *Nostoc* sp., and *Lyngbya majuscule* offers great opportunity and a platform for the discovery of anticancer and antitumor agents. Furthermore, a few have focused on baseline information for promoting the use of cyanobacterial bioactive compounds as drugs using the computational approach. They can be profitable to mankind in multidirectional ways and probably they constitute a principal group of organisms for biotechnological exploitation, especially for valuable products, processes and services, with significant impact in food and pharmaceutical industries as well as in public health. However, still the active principles and their mode of action are yet unknown in most cases. Since there is a direct need for an alternate antimicrobial drug due to the emergence of multi drug resistant pathogens throughout the Globe, as one of the major concerns. Literature stresses the study of emerald compound of algae including Cyanobacteria having antimicrobial property. The search of new active substances with antimicrobial activity from Sub-aerial Cyanobacteria (BGA) of extreme environments, form a major group among algae too are the potential and promising candidates. It is of its kind to mention here that, In the past [33] a number of sub-aerial Cyanobacteria from old temples, monuments, caves, building facades were isolated to accelerate their survival strategies and control mechanisms; only few made an effort for their bioactivity [55]. Few are proved to be antiviral drug, anticancer drug, antibacterial drug and or antifungal drug too [112, 113]. In this review, ten major activities of sub-aerial cyanobacteria have been listed from the literature (anticyanobacterial, antialgal, antibacterial and antimicrobial activities) as describe in **Table 2**. However, to the best of knowledge these sub-aerial Cyanobacteria of unique environment are not explored for their biotechnological applications in terms of bioactivities and/or antimicrobial activities to find out their possible use in pharmaceuticals for development of new antimicrobial compounds which need to be further analyzed.

5. Conclusion

Nowadays, the production of secondary metabolites from extreme enduring cyanobacteria has catapulted this group of organisms into the midst of intense research. The survival strategies of cyanobacteria to various stress fixed secondary metabolites sources in term of growth, physiology and different metabolic processes are of great interest as they able to secrete different metabolites with environmental stress and ability for their adaptation to extreme environments. No systematic scientific approach has been taken yet on secondary metabolite with their antimicrobial properties from sub-aerial cyanobacteria in India or other countries on this subject. A few research workers have worked on the bioactive compound and their approaches in pharmaceutical sectors of these sub-aerial cyanobacteria to represent as a new source of biologically active compounds in the form of secondary metabolites with production of different antimicrobial compounds, further more studies are desired to find its way for use in pharmaceutical industries, for development of newer antimicrobials, against costly harmful antibiotics and chemotherapeutics, in order to enjoy the benefits and/or the fruits of this investigation for future uses. However, this knowledge may be important in developing strains of sub-aerial cyanobacteria with higher efficiency for antimicrobial properties.

Funding

No funding was received for this contribution.

Conflicts of interest

The author declares no conflict of interest.

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References

[1] Pratt R, Daniels TC, Eiler JB, Gunnison JB, Kumler WD. Chlorellin, an antibacterial substance from *chlorella*. Science. 1944;**99**(2754):351-352

[2] Guiry MD, Guiry GM. AlgaeBase. World-wide electronic publication. Galway: National University of Ireland; 2020. https://www.algaebase.org. 2020

[3] Singh R, Parihar P, Singh M, Bajguz A, Kumar J, Singh S, et al. Uncovering potential applications of cyanobacteria and algal metabolites in biology, agriculture and medicine: Current status and future prospects. Frontiers Microbiology. 2017;**8**:515

[4] Dixit RB, Suseela MR. Cyanobacteria: Potential candidates for drug discovery. Antonie Van Leeuwenhoek. 2013;**103**(5):947-961

[5] Gaysina LA, Saraf A, Singh P. Cyanobacteria in diverse habitats. In: Mishra AK, Tiwari DN, Rai AN, editors. Cyanobacteria from Basic Science to Application. Academic Press; 2019. pp. 1-28

[6] Ferrari C, Santunione G, Libbra A, Muscio A, Sgarbi E, Siligardi C, et al. Review on the influence of biological deterioration on the surface properties of building materials: Organisms, materials and methods. International Journal of Design & Nature and Ecodynamics. 2015;**10**(1):21-39

[7] Drovac-cik AV, Dulic TI, Stojanovic DB, Svircev ZB. The importance of extremophiles cyanobacteria in the production of biologically active compounds. Natural Product Sciences. 2007;**112**:57-66

[8] Rastogi RP, Incharoensakdi A. Characterization of UV-screening compounds, mycosporine-like amino acids, and scytonemin in the cyanobacterium *Lyngbya* sp. CU2555. FEMS Microbiology Ecology. 2013;**8**(1):254-256

[9] Rezayian M, Niknam V, Ebrahimzadeh H. Oxidative damage and antioxidative system in algae. Toxicology Reports. 2019;**6**:1309-1313

[10] Böhm GA, Pfleiderer W, Böger P, Scherer S. Structure of a novel oligosaccharide mycosporine amino acid ultraviolet a/B sunscreen pigment from the terrestrial cyanobacterium *Nostoc commune*. Journal of Biological Chemistry. 1995;**270**:8536-8539

[11] Sinha RP. Klisch M, Helbling EW, H€ader DP. Induction of mycosporine-like amino acids (MAAs) in cyanobacteria by solar ultraviolet radiation. Journal of Photochemistry and Photobiology B: Biology. 2001;**6**:129-135

[12] Anagnostidis K, Economou-Amilli A, Roussomoustakaki M. Epilithic and chasmolithic microflora (Cyanophyta, Bacillariophyta) from marbles of the Parthenon-acropolis, Athens, Greece. Nova Hedwigia. 1983;**38**:227-288

[13] Saiz-Jimenez C, Hermosin B, Ortega-Calvo JJ, GómezAlarcón G. Applications of analytical pyrolysis to the study of stony cultural properties. Journal of Analytical and Applied Pyrolysis. 1991;**20**:239-521

[14] Ortega-Calvo JJ, Sanchez-Castillo PM, Hernandez-Marine M, Saiz-Jimenez C. Isolation and characterization of epilithic chlorophyta and cyanobacteria from two Spanish cathedrals (Salamanca and Toledo). Nova Hedwigia. 1993a;**57**:239-253

[15] Ortega-Calvo JJ, Hernandez-Marine M, Saiz-Jimenez C. Cyanobacteria and algae on historic buildings and monuments. In: Garg KL, Garg N, Mukerji NG. editors. Recent Advances in Biodeterioration and Biodegradation Calcutta: Naya Prokash; 1993b. pp. 173-203

[16] Gómez-Alarcón G, Muñoz M, Ariño X, Ortega-Calvo JJ. Microbial communities in weathered sandstones: The case of Carrascosa del campo church. Spain. Science of the Total Environment. 1995;**167**:249-254

[17] Zurita YP, Cultrone G, Castillo PS, Sebastián E, Bolívar FC. Microalgae associated with deteriorated stonework of the fountain of Bibatauín in Granada. Spain. International Biodeterioration and Biodegradation. 2005;**55**:55-61

[18] Uher B, Aboal M, Kovacik L. Epilithic and chasmoendolithic phycoflora of monuments and buildings in South-Eastern Spain. Cryptogamie Algologie. 2005;**26**:275-358

[19] Gaylarde PM, Gaylarde CC. Algae and cyanobacteria on painted buildings in Latin America. International Biodeterioration and Biodegradation. 2000;**46**:93-97

[20] Crispim CA, Gaylarde PM, Gaylarde CC. Algal and cyanobacterial biofilms on calcareous historic buildings. Current Microbiology. 2003;**46**:79-82

[21] Barberousse H, Tell G, Yéprémian C, Couté A. Diversity of algae and cyanobacteria growing on buildings facades in France. Algological Studies. 2006;**120**:81-105

[22] Tomaselli L, Lamenti G, Bosco M, Tiano P. Biodiversity of photosynthetic micro-organisms dwelling on stone monuments. International Biodeterioration and Biodegradation. 2000a;**46**:251-258

[23] Tomaselli L, Tiano P, Lamenti G. Occurrence and fluctuation in photosynthetic biocoenoses dwelling on stone monuments. In: Ciferri O, Tiano P, Mastromei G. editors. The Role of Microbial Communities in the Degradation and Protection of Cultural Heritage. New York: Kluwer; 2000b. pp. 63-76

[24] Lamenti G, Tiano P, Tomaselli L. Biodeterioration of ornamental marble statues in the Boboli gardens (Florence, Italy). Journal of Applied Phycology. 2000;**12**:427-433

[25] Bellinzoni AM, Caneva G, Ricci S. Ecological trends in travertine colonization by pioneer algae and plant communities. International Biodeterioration and Biodegradation. 2003;**51**:203-210

[26] Ortega-Calvo JJ, Ariño X, Hernandez-Marine M, Saiz-Jimenez C. Factors affecting the weathering and colonization of monuments by phototrophic microorganisms. Science of the Total Environment. 1995;**167**:329-341

[27] Oliveira BP, Rosa JM, Miller AZ, Saiz-Jimenez C. An integrated approach to assess the origins of black films on a granite monument. Environmental Earth Science. 2011;**63**:1677-1690

[28] Uher B, Kováčik L. Epilithic cyanobacteria and algae in subterrean mausoleum Chatam Sófer. Bulletin of Slovakia Botanical Spoločnkia, Bratislava. 2004;**10**:83-86

[29] Uher B. Spatial distribution of cyanobacteria and algae from the tombstone in a historic cemetery in Bratislava, Slovakia. Fottea. 2008;**9**:81-92

[30] Tripathy P, Roy A, Adhikary SP. Survey of epilithic blue green algae (cyanobacteria) from temples of India and Nepal. Archives für Hydrobiology Supplement Algological Studies. 1997;**87**:43-57

[31] Tripathy P, Roy A, Anand N, Adhikary SP. Blue-green algae flora of rock surface of temples and monuments of India. Feddes Repertorium. 1999;**110**:133-144

[32] Pattanaik B, Adhikary SP. Blue-green algal flora of some archeological site and monuments of India. Feddes Repertorium. 2002;**113**:289-300

[33] Samad LK, Adhikary SP. Diversity of micro-algae and cyanobacteria on building facades and monuments in India. Algae. 2008;**23**(2):91-114

[34] Sahu JK, Nayak B, Pradhan P, Bhattacharyya S. Epilithic cyanobacteria on temples of Western Odisha. A Scientific Journal of Biological Sciences. 2011;**2**(1&2):47-50

[35] Khan AB, Kulathuran G. Composition of microorganisms in deterioration of stone structures of monuments. The Bioscan. 2010;**1**:57-67

[36] Karande VC, Uttekar GV, Kamble KB, Karande CT. Diversity of cyanobacteria in biofilms on buiding facades of Western Maharashtra. Phykos. 2012;**42**(2):54-58

[37] Keshari N, Adhikary SP. Diversity of cyanobacteria on stone monuments and building facades of India and their phylogenetic analysis. International Biodeterioration and Biodegradation. 2014;**90**:45-51

[38] Pradhan P, Bhattacharyya S, Deep PR, Sahu JK, Nayak B. Biodiversity of Cyanoprokaryota from monuments of Western Odisha, India-I (Chroococales and Stigonematales). Phykos: Journal of the Phycological Society. 2018;**48**(1):58-66

[39] Pattnaik S, Singh L. Cyanobacteria bioactive compound, their production and extraction with pharmaceutical application - a review. International Journal of Current Microbiology and Applied Science. 2020;**9**(6):3394-3405

[40] Pandey VD. Cyanobacterial natural products as antimicrobial agents. International Journal of Current Microbiology and Applied Science. 2015;**4**(1):310-317

[41] Sethubathi GVB, Prabu VA. Antibacterial activity of cyanobacterial species from Adirampattinam coast, southeast coast of palk bay. Current Research Journal of Biological Sciences. 2010;**2**(1):24-26

[42] Engene N, Paul VJ, Byrum T, Gerwick WH, Thor A, Ellisman MH. Five chemically rich species of tropical marine cyanobacteria of the genus *Okeania* gen. Nov. (Oscillatoriales, Cyanoprokaryota). Journal of Phycology. 2013;**49**(6):1095-1106

[43] Skočibušić M, Lacić S, Rašić Z. Evaluation of antimicrobial potential of the Marine cyanobacterium. *Rivularia mesenterica*. Journal of Advances in Microbiology. 2019;**16**(4):1-11

[44] 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

[45] Mugilan V, Sivakami R. Antimicrobial activity of microalgae isolated from fresh water pond, Tamil

Nadu, India. International Journal of Current Microbiology and Applied Sciences. 2016;**5**(6):588-595

[46] Yadav S, Agrawal M, Raipuria N, Agrawal MK. Antimicrobial activity of *Nostoc calcicola* (cyanobacteria) isolated from Central India against human pathogens. Asian Journal of Pharmaceutics. 2016;**10**(6):554-558

[47] Nagaranjan M, Maruthanayagam V, Sundararaman M. SAR analysis and bioactive potentials of freshwater and terrestrial cyanobacterial compounds: A review. Journal of Applied Toxicology. 2013;**33**(5):313-349

[48] Srikong W, Mittraparp-arthorn O, Rattanaporn P, Bovornreungroj N. Antimicrobial activity of seaweed extracts from Pattani, southeast coast of Thailand. Food and Applied Bioscience Journal. 2015;**3**(1):39-49

[49] Fish SA, Codd GA. Bioactive compound production by thermophilic and thermotolerant cyanobacteria (blue-green algae). World Journal of Microbiology and Biotechnology. 1994;**10**:338-341

[50] Sherwani N, Abed Raeid MM, Dobretsov S, Mary S. Antibacterial and antifungal activities of cyanobacterial strains isolated from hot springs in Oman. Journal of Sciences. 2015;**20**(1):11-19

[51] Swain SS, Paidesetty SK, Padhy RN. Antibacterial, antifungal and antimycobacterial compounds from cyanobacteria. Biomedicine and Pharmacotherapy. 2017;**90**:760-776

[52] Ramya VP, Muralitharan G. Evaluation of antibacterial activity of cyanobacteria isolated from freshwater ecosystem of Tiruchirappalli district, Tamil nadu, India. Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences. 2019;**5**(2):331-344

[53] Kumar S, Marketo M, Andreja K, Katrina D, Jan H, Hrouzek P. Antimicrobial activity and bioactive profiling of heterocystous cyanobacterial strains using MS/MS-based molecular networking. Folia Microbiologia. 2019;**64**:645-654

[54] Shaieb FA, Issa AAS, Meragaa A. Antimicrobial activity of crude extracts of cyanobacteria *Nostoc commune* and *Spirulina platensis*. Archives of Biomedical Sciences. 2014;**2**(2):34-41

[55] Yadav S, Agrawal M, Raipuria N, Agrawal MK. Potential of cyanobacteria collected from Central India against human pathogenic bacteria-*In vitro*. International Journal of Pharmaceutical Sciences and Research. 2015;**6**(9):4047-4052

[56] 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

[57] Mazur-Marzec H, Ceglowska M, Konel R, Pyrć K. Antiviral cyanometabolites - a reviews. Biomolecules. 2021;**11**:474

[58] Semary NA, Fouda M. Anticancer activity of *Cyanothece* sp. strain extracts from Egypt: First record. Asian Pacific Journal of Tropical Biomedicine. 2015;**5**(12):992-995

[59] Karan T, Aydin A. Anticancer potential and cytotoxic effect of some freshwater cyanobacteria. Tropical Journal of Pharmaceutical Research. 2018;**17**(11):2183-2188

[60] Silva MR, Silva GM, Silva A, Lima L, Bezerra R, Marques D. Bioactive

compounds of *Arthrospira* spp. (*spirulina*) with potential anticancer activities: A systematic review. ACS Chemical Biology. 2021;**16**(11): 2057-2067

[61] Vijaykumar S, Menakha M. Pharmaceutical applications of cyanobacteria- a review. Journal of Acute Medicine. 2015;**5**(1):15-23

[62] Singh RK, Tiwari SP, Rai AK, Mohapatra TM. Cyanobacteria: An emerging source for drug discovery. The Journal of Antibiotics. 2011;**64**(6):401-412

[63] Shishido TK, Humisto A, Jokela J, Liu L, Wahlsten M, Tamrakar A, et al. Antifungal compounds from cyanobacteria. Marine Drugs. 2015;**13**(4):2124-2214

[64] Marrez DA, Sultan YY. Antifungal activity of the cyanobacterium *Microcystis aeruginosa* against mycotoxigenic fungi. Journal of Applied Pharmaceutical Science. 2016;**6**(11):191-198

[65] Rath B, Priyadarshini I. Antibacterial and antifungal activity of marine cyanobacteria from Odisha coast. International Journal of Current Treasure Research. 2013;**2**(1):248-251

[66] Saad MH, El-Fakharany EM, Salem MS, Sidkey NM. The use of cyanobacterial metabolites as natural medical and biotechnological tools: Review article. Journal of Biolmolecular Structure and Dynamics. 2020;**8**:1-23

[67] Zahra Z, Choo DH, Lee H, Parveen A. Cyanobacteria: Review of current potentials and applications. Environments. 2020;**7**(13):1-17

[68] Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nature Reviews Drug Discovery. 2005;**4**(3):206-220

[69] Guaadaoui A, Benaicha S, Elmajdoub N, Bellaoui M, Hamal A. What is a bioactive compound? A combined definition for a preliminary consensus. International Journal of Nutrition and Food Sciences. 2014;**3**(3):174-179

[70] Walton K, Berry JP. Indole alkaloids of the Stigonematales (Cyanophyta): Chemical diversity, biosynthesis and biological activity. Marine Drugs. 2016;**14**(73):1-28

[71] Ishida K, Matsuda H, Murakami M, Yamaguchi K. Kawaguchipeptin B, an antibacterial cyclic undecapeptide from the cyanobacterium Microcystis aeruginosa. Journal of Natural Product. 1997;**60**(7):724-726

[72] Smitka TA, Bonjouklian R, Doolin L, Jones ND, Deeter JB, Yoshido WY, et al. Ambiguine isonitriles, fungicidal hapalindole-type alkaloids from three genera of blue green algae belonging to the Stigonemataceae. Journal of Organic Chemistry. 1992;**57**:857-861

[73] Raveh A, Carmeli S. Antimicrobial ambiguines from the cyanobacterium *Fischerella* sp. collected in Israel. Journal of Natural Products. 2007;**70**(2):196-201

[74] Mo S, Krunic A, Pegan SD, Franzblau SG, Orijala J. An antimicrobial guanidine-bearing sesterterpene from the cultured cyanobacterium *Scytonema* sp. Journal of Natural Products. 2009;**72**(11):2043-2045

[75] Neuhof T, Schmieder P, Preussel K, Dieckmann R, Pham H, Bartl F, et al. Hassallidin a, a glycosylated lipopeptide with antifungal activity from the cyanobacterium *Hassallia* sp. Journal of Natural Products. 2005;**68**(5):695-700

[76] Pignatello JJ, Porwoll J, Carlson RE, Xavier A, Gleason FK, Wood JM. Structure of the antibiotic cyanobacterin, a chlorine-containing gamma lactone from the freshwater cyanobacterium *Scytonema hofmanni*. Journal of Organic Chemistry. 1983;**48**(22):4035-4038

[77] Stewart JB, Bornemann V, Chen JL, Moore RE, Caplan FR, Karuso H, et al. Cytotoxic, fungicidal nucleosides from blue green algae belonging to the Scytonemataceae. Journal of Antibiotics. 1988;**41**:1048-1056

[78] Miao SC, Anderson RJ, Allen TM. Cytotoxic metabolites from the sponge *Ianthella basta* collected in Papua New Guinea. Journal of Natural Products. 1990;**53**(6):1441-1446

[79] Ma LX, Led JJ. Determination by high field NMR spectroscopy of the longitudinal electron relaxation rate in Cu (II) plastocyaninform *Anabaena variabilis*. Journal of American Chemical Society. 2000;**122**:7823-7824

[80] Bonjouklian R, Smitka TA, Doolin LE, Molloy RM, Debono M, Shaffer SA, et al. Tjipanazoles, new antifungal agents from the blue green alga *Tolypothrix tjipanasensis*. Tetrahedron. 1991;**47**:7739-7750

[81] Nagatsu A, Kajitani H, Sakakibara J. Muscoride a - a new oxazole peptide alkaloid from freshwater cyanobacterium *Nostoc muscorum*. Tetrahedron Letters. 1995;**36**(23):4097-4100

[82] Hagmann L. Jüttner F, Fischerellin A. a novel photosystem-II inhibiting allelochemical of the cyanobacterium *Fiseherella museieola* with antifungal and herbicidal activity. Tetrahedron Letters. 1996;**37**:6539

[83] Kajiyama S, Kanazaki H, Kawazu K, Kobayashi A. Nostifungicide, an antifungal lipopeptide from the field grown terrestrial blue-green alga. Tetrahedron Letters. 1998;**39**:37-40

[84] Jaki B, Orjala J, Heilmann J, Linden A, Vogler B, Sticher O. Novel extracellular diterpenoids with biological activity from the cyanobacterium *Nostoc commune*. Journal of Natural Products. 2000;**63**(3):339-343

[85] Hirata K, Yoshitomi S, Dwi S, Iwabe O, Mahakhant A, Polchai J, et al. Bioactivities of nostocine a produced by a fresh water cyanobacterium nostoc spongiaefrome TISTR 8169. Journal of Bioscience and Bioengineering. 2003;**95**:512-517

[86] Park A, Moore RE, Patterson GML. Fischerindole L, a new isonitrile from the terrestrial blue-green alga *Fischerella muscicola*. Tetrahedron Letters. 1992;**33**:3257-3260

[87] Ghasemi Y, Yazdi MT, Shafiee A, Amini M, Shokravi S, Zarrini G. Parsiguine, A Novel Antimicrobial Substance from *Fischerella ambigua*. Pharmaceutical Biology. 2004;**42**(4-5):318-322

[88] Kim H, Krunie A, Lantvit D, Shen Q, Kroll DJ, Swanson SM, et al. Nitrile containing fischerindoles from the cultured cyanobacterium *Fischerella* sp. Tetrahedron. 2012;**68**:3205-3209

[89] Patterson GML, Bolis CM. Scytophycin production by axenic cultures of the cyanobacterium *Scytonema oscellatum*. Natural Toxins (USA). 1997;**2**:280-285

[90] Ishibashi M, Moore RE, Patterson GML, Xu C, Clardy J. Scytophycins, cytotoxic and animycotic agents from cyanophyte *Scytonema pseudohofmanii*. Journal of Organic Chemistry. 1986;**51**:5300-5306

[91] Gleason FK, Baxa CA. Activity of the natural algicides, cyanobacterin, on eukaryotic microorganisms. FEMS Microbiology Letters. 1986;**33**:85-88

[92] Doan NT, Rickards RW, Rothschild JM, Smith GD. Allelopathic actions of the alkaloid 12-epi-hapalindole E isonitrile and calothrixin a from cyanobacteria of the genera *Fischerella* and *Calothrix*. Journal of Applied Phycology. 2000;**12**:409-416

[93] Asthana RK, Deepali S, Tripathi MK, Srivastava A, Singh AP. Isolation and identification of a new antibacterial entity from the Antarctic cyanobacterium *nostoc* CCC 537. Journal of Applied Phycology. 2009;**21**:81-88

[94] Chinnu K, Muthukumaran M, Mukund S, Sivasubramanian V. Antimicrobial and antifungal activity of isolated betaglucan from *Chroococcus turgidus*. Indian Journal of Pharmaceutical Science & Research. 2014;**4**(4):217-220

[95] Shin MS, Lee S, Lee KY, Lee HG. Structural and biological characterization of aminated-derivatized oat β-glucan. Journal of Agriculture and Food Chemistry. 2005;**53**(14):5554-5558

[96] Flores E, Wolk CP. Production, by filamentous, nitrogen- fixing cyanobacteria, of a bacteriocin and of other antibiotics that kill related strains. Archives of Microbiology. 1986;**145**(3):215-219

[97] Volk RB. Screening of microalgal culture media for the presence of algicidal compounds and isolation and identification of two bioactive metabolites excreted by the cyanobacteria *Nostoc insulare* and *Nodularia harveyana*. Journal of Applied Phycology. 2005;**17**(4):339-347

[98] Vestola J, Shishido TK, Jokela J, Fewer DP, Aitio O, Permi P, et al. Hassallidins, antifungal glycolipopeptides, are wide spread among cyanobacteria and are the end-product of a non-ribosomal pathway. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**:E1909-E1917

[99] Seddek NH, Fawzy MA, El-Said WA, Ragaey MM. Evaluation of antimicrobial, antioxidant and cytotoxic activities and characterization of bioactive substances from freshwater blue-green algae. Global NEST Journal. 2019;**21**(3):329-337

[100] Amaral R, Fawley KP, Němcová Y, Ševčíková T, Lukešová A, Fawley MW, et al. Toward modern classification of Eustigmatophytes, including the description of Neomonodaceae fam. Nov. and three new genera. Journal of Phycology. 2020;**56**(3):630-648

[101] Lamprinou V, Tryfinopoulou K, VelonakisEN,VatopoulosA,AntonopoulouS, Fragopoulou E, et al. Cave cyanobacteria showing antibacterial activity. International Journal of Speleology. 2015;**44**(3):1-9

[102] Panigrahi S, Sethi AK, Samad LK. Antibacterial activities of *Scytonema hofman* extracts against human pathogenic bacteria. International Journal of Pharmacy and Pharmaceutical Science. 2015;**7**(5):123-126

[103] Pattnaik S, Samad LK. Spectral analysis of biologically active compounds and antibacterial activity of *Scytonema ocellatum* isolated from sub-aerial habitats. International Journal of Current Research. 2018;**10**(9):73218-73224

[104] Bhakat S, Saha S, Mandal S, Rath J. Antibacterial activity of desiccated cyanobacterium *Anabaena* sp. isolated from Terracotta Monuments of

Bishnupur, West Bengal. International Journal of Pharmaceutical Science and Drug Research. 2020;**12**(2):1333

[105] Pattnaik S, Rath CC, Singh L. Isolation, identification and screening for bioactive compounds with antimicrobial activities from sub-aerial cyanobacteria of eastern regions, Odisha. International Journal of Pharmaceutical Sciences and Research. 2021;**12**(7):3716-3730

[106] Pattnaik S, Mishra BB, Singh L. Isolation and characterization of a novel antimicrobial compound from sub-aerial cyanobacterium *Fischerella* sp., isolated from building facades. Applied Biological Research. 2021;**23**(1):1-12

[107] Luesch H, Moore RE, Paul VJ, Mooberry SL, Corbett TH. Isolationof dolastatin 10 from the marine cyanobacterium Symploca species VP642 and total stereochemistry and biological evaluation of its analogue symplostatin 1. Journal of Natural Product. 2001a;**64**:907-910

[108] Edelman MJ, Gandara DR, Hausner P, Israel V, Thornton D, DeSanto J, et al. Phase 2 study of cryptophycin 52 (LY355703) in patients previously treated with platinum-based chemotherapy for advanced non-small cell lung cancer. Lung Cancer. 2003;**39**:197-199

[109] D' Agostino G, Del Campo J, Mellado B, Izquierdo MA, Minarik T, Cirri L, et al. A multicancer phase in study of the cryptophycin analog LY355703 in patients with platinum-resistant ovarian cancer. International Journal of Gynecology Cancer. 2006; **16**:71-76

[110] Sammet B, Bogner T, Nahrwold M, Weiss C, Sewald N. Appeoaches for the synthesis of functionalized cryptophycins. Journal of Organic Chemistry. 2010;**75**:6953-6960

[111] Weiβ C, Bogner T, Sammet B, Sewald N. Total synthesis and biological evaluation of fluorinated cryptophycins. Beilstein Journal of Organic Chemistry. 2012;**8**:2060-2066

[112] Lingington RG, Clark BR, Trimble EE, Almanza A, Urina LD, Kyle DE, et al. Antimalarial peptides from marine cyanobacteria: Isolation and structural elucidation of gallianamide a. Journal of Natural Products. 2009;**72**(1):14-17

[113] Abdo SM, Hetta MH, El-Senousy WM, El Din RAS, Ali GH. Antiviral activity of freshwater algae. Journal of Applied Pharmaceutical Science. 2012;**2**(2):21-25