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CYANOBACTERIA: A POTENT SOURCE OF NOVEL BIO-ACTIVE COMPOUNDS

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ABSTRACT
Cyanobacteria are a rich source of novel bioactive compounds with a broad spectrum of biological activities. Cyanobacteria produce many biologically active chemicals, although only a small fraction of these molecules have been identified and characterized in the last several decades. They exhibit a range of bioactivities, including antimicrobial, anticancer, antiviral, and antimalarial. They synthesized non-ribosomal peptides through non-ribosomal peptide synthetase (NRPs), which are multimodular enzyme complexes via ribosome-independent pathways. Several methods have been standardized for isolation, purification and characterization of cyanobacterial bioactive compounds. This paper provides a comprehensive review of cyanobacterial bioactive compounds, including antibacterial, antiviral, antiprotozoal, and anticancer compounds, as well as biosynthesis and extraction techniques from cyanobacteria, in response to the high demand for novel bioactive compounds.

Keywords: Cyanobacteria, Antibacterial, Antiviral, Antiprotozoal, Anticancer, Bioactive compounds.

1. INTRODUCTION
Drug resistance is a serious problem among organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) (Reynolds et al. 2004; Qureshi et al. 2021b; Qureshi et al. 2021a; Qureshi et al. 2022), penicillin-resistant *Streptococcus pneumoniae* (Karchmer 2004), and *Pseudomonas aeruginosa* (Paterson 2006). This indicates that conventional antibiotics have lost efficacy, necessitating their substitution with newer medications. These factors together lead to the search for novel drugs and may be new sources, as many unexplored bacteria create powerful bioactive compounds. Only 1-10 % of cultivated bacteria (2 x 10^5) have been studied (Cowan 2000)**.** It is anticipated that uncultured bacteria and the vast microbial diversity would provide additional sources of antibiotics. (Clardy et al. 2006).

Microorganisms, including actinobacteria, bacteria and fungi, have been explored widely over many decades, and many drugs have been originally isolated and characterized. Among the microorganisms, actinomycetes produced a tremendous amount of bioactive compounds of diverse nature (Selim et al. 2021). Bioactive compounds are secondary metabolites that do not function in the growth or reproduction of living organisms (animals, plants and microbes) (Yang et al. 2016). They have a wide range of chemical and structural diversity, such as steroids, terpenoids, alkaloids, polyketides, phenolic compounds etc., and exhibit diverse biological activity (Sytar and Smetanska 2022). For the development of pharmaceutical products, this is the most fruitful source. Approximately one hundred innovative products are now being evaluated in clinical trials, mostly as anticancer and anti-infective therapies (Harvey et al. 2015). Adoption of sophisticated techniques increased the probability that novel drugs derived from bacteria, actinomycetes, or yeasts will be more broadly accessible (Newman and Cragg 2012; Harvey et al. 2015). The bulk of pharmaceuticals on the market are derived from actinomycetes or fungi.

Cyanobacteria are photosynthetic, oxygen-evolving, Gram-negative prokaryotes found in every environment, including freshwater, saline and most adverse conditions (Ward et al. 2012; Yadav et al. 2022). They are found in different environmental conditions, from symbiotic, aquatic, saline, deserts, terrestrial and hot springs (Whitton and Potts 2012). Cyanobacteria contain some specialized structure, heterocyst, and the ability to fix atmospheric nitrogen. However, few cyanobacteria, mainly marine nitrogen-fixing cyanobacteria, are capable to fixed molecular nitrogen without heterocyst (Díez et al. 2008). The cyanobacteria's dispersion and colonization occur by a specialized structure known as hormogonia(Meeks et al. 2002).

Cyanobacteria are promising organisms that produce novel biochemically active chemicals known as bioactive compounds (Singh et al. 2005; Gayakwad et al. 2015; Singh et al. 2017; Begum et al. 2022; Singh et al. 2022). Several genera of cyanobacteria, including *Limbia, Microcystis, Oscillatoria,* and *Nostoc*, can synthesize bioactive chemicals (Selim et al. 2021). They potentially produce bioactive molecules essential to their ecosystems. Recent literature shows that 90 genera of cyanobacteria have synthesized bioactive compounds. Most of these organisms belong to the orders *Chroococcales, Synechococcales, Oscillatoriales,* and *Nostocales*. On the other hand, *Pleurocapsales, Chroococcidiopsale* and *Gloeobacterale* are unexplored or partially explored (Demay et al. 2019). They mainly exhibited different types of activity such as antibacterial (Reichelt and Borowitzka 1984; Cannell et al. 1987), antifungal (Kellam and Walker 1989; Hagmann and Jüttner 1996), anticancer (Carmeli et al. 1990; Kashiwagi et al. 2005)**,** antiviral (Starr and Moran 1962; Gupta et al. 2014), and antiprotozoal compounds (Broniatowska et al. 2011).

The bioactive molecules formed within the cell biomass are referred to as end metabolites. Exo-metabolites, on the other hand, are bioactive compounds that are produced in reaction to the environment (De Morais et al. 2015). Among the several bioactive secondary endo-metabolites identified from cyanobacteria is the cytotoxic lyngbyabellin from *Lyngbya majuscula* (Han et al. 2005), pahayokolide A (anticancer) from *L. semiplena* (Berry et al. 2017), hapalindole series (antituberculosis) (Mayer et al. 2016), venturamide A, B (antimalarial) from *Oscillatoria* sp. (Linington et al. 2008) and antimalarial linear lipopeptides from the marine *L. majuscula* (McPhail et al. 2007).

1.1 Antimicrobial compounds

Chemicals that kill or inhibit microorganisms such as bacteria, fungi, and protozoa are known as antimicrobial compounds. Antimicrobial drugs are selective, killing or inhibiting the growth and proliferation of bacteria (Hood and Khan 2020)**.** Secondary metabolites are produced at a certain cell age and are affected by biotic and abiotic stimuli (Ramakrishna and Ravishankar 2011). The nature of the substances varies depending on the circumstances, e.g. antibacterial in the case of bacterial pathogens, antiviral, antiprotozoal, etc. Cyanobacteria are the richest source of antibacterial compounds that belongs to a diverse chemical class, including alkaloids, fatty acids, and terpenoid. Nonetheless, a significant variety of additional substances, including macrolides, peptides, aromatic compounds, indole paracyclophanes, and others, have also been identified (Rojas et al. 2020).

Table 1 lists the antimicrobial compounds found in cyanobacteria and their biological effects. Ambiguine isonitrile A is an indole alkaloid isolated from *Fischerella ambigua* (UTEX 1903) and found to have antibacterial activity against *Mycobacterium* and *Bacillus anthracis* (Jaki et al. 2000; Mo et al. 2009)**.** The terrestrial cyanobacterium *Nostoc commune* excreted diterpenoid molecule in the extracellular medium, identified as Noscomin, exhibits antibacterial activity against *Staphylococcus, Escherichia coli* and *Bacillus cereus*. *Fischerella ambigua* synthesized and secreted spent medium. Characterization of the bioassay-directed fraction parsiguine displayed antibacterial and antifungal properties (Ghasemi et al. 2004). Hapalindole-T was isolated from an organic solvent extract of *Fischerella* sp. extracted from *Azadirachta indica* (Neem bark) and showed antibacterial activity against *Mycobacterium tuberculosis*, *Enterobacter aerogenes*, *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi*, and *Escherichia coli* (Asthana et al. 2006).

Table 1. Antmicrobial compounds synthesized by cyanobacteria

S.N	Compounds	Biochemical Nature	Cyanobacteria	Activity against	References
1.	Noscomin	Diterpenoid	*Nostoc commune*	*E. coli* *B. cereus*	Jaki et al. (2000)
2.	Hapalindole-T	Diterpenoid	*Fischerella* sp	*M. tuberculosis, E. aerogenes, S. aureus, P. aeruginosa, S. typhi, E. coli*	Asthana et al.(2006)

3.	Cryptophycin	Desipeptide	*Nostoc* ATCC 53789	*Armillaria* sp. *S. sclerotiorum*	Schwartz et al. (1990)
4.	Scytoscalarol	Sesterterpene	*Scytonema* sp.	*B. anthracis*, *S. aureus*, *E.coli*, *C. albicans* *M. tuberculosis*	Mo (2009)
5.	Lyngbyazothrins	peptides	*Lyngbya* sp	*B. subtilis*, *E. coli*, *P. aeruginosa*, and *S. marcescens*	Asthana et al. (2009)
6.	Anachelin H	Peptides	*Anabaena cylindrica*	*M. catarrhalis*	Gademann (2007)
7.	Anabaenopeptins A	Peptides	*Anabaena flos-aquae*	*M. catarrhalis*	Harada *et al.* (2004).

Cryptophycin was produced by the cyanobacterium *Nostoc* strain ATCC 53789, and its methanolic extract exhibited antifungal (*Armillaria* sp. *Sclerotinia sclerotiorum*), nematocidal (*Caenorhabditis elegans*), and cytotoxic (*Artemia salina*) activity, but no antibacterial activity (Biondi et al. 2008). Therefore, this cyanobacterium is utilized as a source of pesticides in the agriculture sector and is beneficial for the overcome its chemical toxicity in soil, plants, and non-target organisms. (Fan et al. 2013) noticed that photosynthetic pigments phycocyanin was extracted from *Anabaena cylindrica*, and it exhibits antibacterial activities on *Bibrio parahemolyticus*, *Bacillus mucilaginosus* and *Sarcina lutea*. Bioassay-guided fractionation was used to extract scytoscalarol, an antimicrobial sesterterpene with a guanidino group isolated from cyanobacterium *Scytonema* sp. (UTEX 1163). *Bacillus anthracis, Staphylococcus aureus, Escherichia coli, Candida albicans*, and *Mycobacterium tuberculosis* were all sensitive to scytoscalarol (Mo et al. 2009). Lyngbyazothrins A, B, C, and D are four novel cyclic undecapeptides isolated from cultivated *Lyngbya* sp. *Lyngbyazothrins* A and B had only modest action against *Micrococcus flavus*, but lyngbyazothrins C and D were effective against *Bacillus subtilis*, *Escherichia coli, Pseudomonas aeruginosa*, and *S. marcescens*.

The bioactive molecule (4-[(5-carboxy-2-hydroxy)-benzyl]-8, 10-dihydroxy-2, 5, 6, 11, 11-pentamethyloctahydrocyclopenta<a>naphthalene) from the Antarctic cyanobacterium *Nostoc* CCC537 was significantly antibacterial against disease-causing bacteria, including *Mycobacterium tuberculosis* H37Rv and *Salmonella typhi* MTCC 3216, respectively (Asthana et al. 2009).

Microcoleous lacustris produced two abietane diterpenes that were effective against *Staphylococcus aureus, Staphylococcus epidermidis*, and *Vibrio cholerae*, but not other bacteria (Pérez Gutiérrez et al. 2008). The anachelin H produced by *Anabaena cylindrica* is antimicrobial. It has a moderate effect on *Moraxella catarrhalis* and is effective against bacterial and fungal diseases (Gademann et al. 2007). The thermotolerant *Phormidium* strain generated extracellular antimicrobial substances that inhibited the development of Gram-positive and Gram-negative bacteria and fungus in batch cultures (Fish and Codd 1994). The toxic effects of cyanobacterial cyclopeptides, microcystins, and nodularins pose a danger to humans.

Microcystin is a cyclic heptapeptide that has the potential to cause cellular damage when ingested into cells through various transporters such as Anion Transporting Polypeptide system (OATP). Certain OATPs are overexpressed in malignant cells relative to normal tissues, suggesting that microcystin may be a promising target for the development of cancer treatments (Sainis et al. 2010).

1.2 Antiviral Compounds

At the global level, spreading viral diseases such as HIV/AIDS, avian influenza, coronavirus, etc., exhibited fatal consequences for human society. The list of antiviral compound synthesized by cyanobacteria are listed in Table 2. Highly antiretroviral therapy (HAART) is used to control HIV and is approved by Food and Drug Administration (FDA). Therefore, novel drugs are essential requirements for fighting against fatal diseases.

Cyanobacterial origin of antiviral compounds exhibits activity by preventing absorption or penetration and viral replication after entry into cells (Yang et al. 1999) isolated peptides cyanovirin-N (Cv-N) from cyanobacteria, which inhibits HIV to cell fusion. Cv-N (101-amino acid peptide sequence) is an 11kDa protein derived from *Nostoc ellipsosporum*; it binds to gp120 and gp41 and suppresses many HIV and SIV strains (SiV). Calcium spirulan (Ca-Sp) is a sulfated polysaccharide antiviral agent derived from the cyanobacterium *Spirulina platensis's* hot H_2O. These antiviral medications impeded the reproduction of enveloped viruses, including Herpes simplex virus type 1, measles virus, influenza A virus, mumps virus, human cytomegalovirus, and HIV-1 (Hayashi et al. 1996). Antiviral medicines like spirulan were discovered from polysaccharide fractions of *Arthrospira platensis* cyanobacteria. These medicines displayed potent antiviral action against cytomegalovirus, human herpes virus type 6, and HIV-1, although their effect on Epstein-Barr virus and influenza A virus was negligible (Rechter et al. 2006)**.** A polysaccharides antiviral drug 211kDa Nostoflan (Kanekiyo et al. 2005) was isolated from cyanobacterium *Nostoc flagelliforme* and active against the enveloped virus, such as influenza A and HSV, HCMV virus. These antiviral drugs inhibit the adhering of the virus to the cells (Kanekiyo et al. 2007).

In the form of a dietary supplement, *Spirulina platensis*is commonly used, and exhibits antiviral and immune-stimulating properties. The natural extract of *S. platensis* was a potent inhibitor against the enveloped virus by preventing some stages of replications of the virus after penetrations into the cell (Yakoot and Salem 2012). Extracts of polysaccharides from *Gloeocapsa turgidus* and *Synechococcus cedrorum* had more antiviral activity against rabies virus than the herpes-1 virus, but extracts of polysaccharides from *Amorphonostoc punctiforme* exhibited either weak or no antiviral activity against both viruses.

Table 2. Antiviral compounds produced by cyanobacteria

S.No.	Compounds	Biochemical Nature	Cyanobacteria	Activity	References
1	Nostoflan	Acidic polysaccharide	*Nostoc flagelliforme*	Anti-herpes simplex virus	Kanekiyo et al..,(2005)
2.	Ichthyopeptins A	Cyclic depsipeptides	Microcystis ichthyoblabe	Influenza A virus	Zainuddin et al. (2007)
3.	Calcium spirulan	Sulfated polysacchride	*Spirulina platensis*	Anti-HIV	Hayashi et al. (1996)
4.	Cyanovirin	Cyanobacterial protein	*Scytonema varium*	Anti-HIV	Dey et al. (2000)
5.	Scytovirin	Cyanobacterial protein	*Scytonema varium*	Anti-HIV	Xiong et al. (2006)
6.	Sulfoglycolipid	Acylated sulfoglycolipids	*Lyngbya lagerhimii*	Anti-HIV	Loya et al. (1998)

Results concluded that cyanobacterial-derived polysaccharides are effective against animal as well as human viruses (Zheng et al. 2006; Mansour et al. 2011). It was found that exopolysaccharides of halophilic cyanobacterium *Aphanothece halophytica* showed effective antiviral drugs against influenza virus A (H1N1) and 30% reduction of *Diplococcuspneumonia* infection by oral administrations of exopolysaccharides in disease suffering mice (Zainuddin et al. 2002)**.** It was noticed that methanolic extract of genus *Microcystis* including *M. aeruginosa* and *M. ichthyoblabe* showed antiviral activity of influenza A virus. Marine cyanobacteria are natural source of cyclic, linear peptides and depsipeptides and these compounds are protease inhibitors, and exhibits antiviral activity against HIV virus (Musale et al. 2020). Lipid soluble extract of *Spirulina platensis*a and *Lyngbya lagerheimii* shows antiviral agents against Herpes simplex virus (HSV) type 1, identification of extract was confirmed as sulphoquinovosyl diacylglycerols, a potent antiviral agent (Chirasuwan et al. 2009). These compounds inhibit reverse transcriptase, DNA polymerase and telomerase (Gustafson et al. 1989; Gupta et al. 2014)**.** It was also reported that antiviral agent polyketides isolated from *Trichodesmium erythraeum* and these compounds were active against the Chikungunya virus.

Thus, innovative medications are urgently required to combat the world's most severe illnesses. Antiviral substances generated from cyanobacteria are generally bioactive by blocking viral absorption or penetration into cells and inhibiting progeny viruses' reproductive stages following infection.

1.3 Antiprotozoal Activity

According to the World Health Organization, approximately 1.2 billion populations of the world are infected with protozoan diseases such as malaria, leishmaniasis and trypanosomiasis, especially in tropical countries (Simmons et al. 2008). The list of antiprotozoal compounds synthesized by cyanobacteria are listed in Table 3.

Table 3. Antiprotozoal compounds produced by cyanobacteria

S.No.	Compounds	Biochemical Nature	Cyanobacteria	Activity	References
1	Viridamide-A	Lipodepsipeptide	*Oscillatoria nigro virdis*	*P.falciparum L. mexicana*	Simmons et al. (2008)
2.	Viridamide-B	Lipodepsipeptide	*Oscillatoria nigro virdis*	*P.falciparum L. mexicana T.cruzi*	Simmons et al., (2008)
3.	Symplocamide-A	Homodetic cyclic peptide	*Oscillatoria* sp	*P.falciparum*	Linington et al., (2007)
4.	Dragomabin	Lipopeptide	*Lyngbya majuscula*	*P.falciparum*	Mcphail et al. (2007).
5.	Ambigol-A	Polychlorinated triphenyl aromatic compounds	*Fischerella ambigua*	*P.falciparum*	Falach et al.(1993)
6.	Ambigol-B	Polychlorinated triphenyl aromatic compounds	*Fischerella ambigua*	*Trypanosoma rhodesiense*	Falach et al.,(1993)
7.	Ambigol-C	Polychlorinated triphenyl aromatic compounds	*Fischerella ambigua*	*Trypanosoma rhodesiense*	Falach et al.,(1993)

Treatment failures, mainly in the resistance to malaria and leishmaniasis, are associated with the development of resistance by the protozoa (Singh et al. 2014; Qureshi et al. 2021b; Qureshi et al. 2022). Contrary, progress in drug discovery initiatives to combat these diseases is quite slow. The Panamanian International Cooperative Biodiversity Group is researching bioactive chemicals in cyanobacteria to promote the development of effective and cost-efficient therapies for various ailments. Five kinds of antiprotozoal compounds from cyanobacteria were reported by (Singh et al. 2014). Terrestrial cyanobacteria *Nostoc commune* and *Rivularia biasolettiana* showed antiprotozoal activity against *Plasmodium falciparum, Trypanosoma brucei rhodesiense,* and *Leishmania donovani.* Aerucyclamide C and D were isolated and characterized from *Microcystis aeruginosa* PCC 7806 and exhibited antiplasmodial activity. Aerucyclamide B and C were effective against *P. falciparum* and *T. brucei rhodesiense*, respectively. It was found that six new bioactive acyl proline derivatives, tumonoic acids D-I, derived from the cyanobacterium *Blennothrix cantharidosmum* had weak antimalarial properties (Clark et al. 2008). The lipodepsipeptides Viridamides A and B, isolated from the marine cyanobacterium *Oscillatoria nigroviridis* were antiprotozoal.

1.4 Anticancer Compounds

Cyanobacteria synthesized a large number of bioactive compounds which targeted the actin/tubulin filaments in eukaryotes (Jordan and Wilson 1998). The list of antiviral compounds synthesized by cyanobacteria are listed in Table 4.

Table 4. Anticancerous compounds produced by cyanobacteria

S. No.	Compounds	Biochemical Nature	Cyanobacteria	Target Site	References
1	Dolastatin-10	Linear pentapetide	*Leptolyngbya* sp	Inhibition of microtubule Assembly	Kalemkerian et al. (1999)
2	Dolastatin-12	Linear pentapetide	*Symploca* sp	Induced cell cycle arrest at the G2-M phase	Catassi et al. (2006)
3	Curacin-A	Polyketide	*Lyngbya majuscula*	Inhibition of polymerization of tubulin in eukaryotes	Gerwick et al. (1994). Yoo and Gerwick, (1995)
4	Curacin-B	Polyketide	*Lyngbya majuscula*	Inhibitors of microtubule polymerization	Gerwick et al. (1994). Yoo and Gerwick, (1995)
5	Curacin-C	Polyketide	*Lyngbya majuscula*	Inhibitors of microtubule polymerization	Gerwick et al. (1994). Yoo and Gerwick, (1995)
6	Curacin-D	Polyketide	*Lyngbya majuscula*	Colchicines binding and tubulin polymerization inhibitors	Márquez et al. (1998)
7	Veraguamides-A	Hexadepsipeptides	*Symploca* cf. hydnoides	Cytotoxic activity against colon Cervical carcinoma	Salvador et al. (2011).
8	Obyanamide	Cyclodepsipeptde	*Lyngbya confervoides*	Antineoplastic activity	Williams et al. (2002).
9	Malevamide-D	Peptide ester	*Symploca hydnoides*	Antineoplastic activity	Horgen et al. (2002)
10	Majusculamide	Amino acid amide	*Lyngbya majuscula*	Antineoplastic activity	Pettit et al. (2008)
11	Lagunamide-A	Cyclodepsipeptide	*Lyngbya majuscula*	Cytotoxic activity against Murine Leukemia cell lines and antimalarial activity	Tripathi et al. (2010)
12	Lagunamide-B	Cyclodepsipep	*Lyngbya*	Cytotoxic and	Tripathi et

		tide	*majuscula*	antimalarial properties	al (2010)
13	Lagunamide-C	Cyclodepsipeptide	*Lyngbya majuscula*	Cytotoxic , antimalarial and anti-swarming activity	Tripathi et al (2011)
14	Lagunamide-D	Macrocyclic Depsipeptide	*Lyngbya* sp and *Dichothrix* sp.	Induced apoptosis	Luo et al., (2019)
15	Digalactosyldiacylglycerol	Glycerides	*Phormidium tenue*	Antitumerogenic	Tokuda et al. (1996)
16	Caylobolide-B	Macrolactone	*Phormidium* sp.	Cytotoxic	Salvador et al. (2010)
17	Bisebromoamide	Peptide	*Lyngbya* sp	Protein kinase Inhibitors	Teruya et al. (2009)
18	Largazole	Cyclic depsipeptide	*Symploca* sp.	Anticancer properties and osteogenic activities	Taori et al. (2008)
19	Hormothamnin-A	Cyclic undecapeptide	*Hormothamnion enteromorphoides*	Cytotoxicity	Malloy et al. (2012)

Two anticancer compounds Dolastatin 10 and 12, were isolated from *Leptolyngbya* sp. and *Symploca* sp., respectively, and these compounds are linear pentapeptides (Kalemkerian et al. 1999; Catassi et al. 2006). *Lyngbya majuscula* is a rich source of bioactive chemicals from which Curacin A, B, C, and D are manufactured. They possess powerful antiproliferative and antimitotic properties (Nagle et al. 1995). Lyngbyabellin B was extracted from a different species of *L. majuscula* and showed cytotoxic activity against LoVo and KB cell lines. It was reported that two anticancer compounds, Malyngamide 3 and Cocosamides B, are anticancer from *L. majuscula,* and these compounds exhibited poor cytotoxicity against colon and breast cancer (Linington et al. 2008). Cryptophycin inhibited leukemia cell line (L-1210) in a dose-dependent manner and isolated from *Nostoc* sp. (Smith et al. 1994). *Calothrix* sp. is the source of Calothrixin A and B and was extracted from the organic extract. It is a potent inhibitor of human cancer cells of the HeLa cell line (Rickards et al. 1999). Nine variants of Apratoxin, such as A, B, C, D, F, D, E, F and G, were isolated and characterized from *Lyngbya* spp. These variants exhibited potent cytotoxicity against different cancer cell lines of HT-29 colon adenocarcinoma, H-460 lung cancer, HCT-116 colorectal, HeLa cervical carcinoma and KB oral epidermoid (Luesch et al. 2001; Matthew et al. 2008; Pérez Gutiérrez et al. 2008; Tidgewell et al. 2010; Oftedal et al. 2010) evaluated 41 marine cyanobacteria, and are effective against acute myeloid leukemia cell lines. Approximately 50% exhibited apoptosis-inducing activity in the aqueous extract of cyanobacteria. A mixture of cyanobacterial extract acts as a synergistic effect with daunorubicin (anthracycline anticancer drug anticancer) in AML cell lines, and cardiomyoblasts were inhibited. Therefore, marine cyanobacteria are a novel source of antileukemic drugs (Oftedal et al. 2010). Largazole (I) is a macrocyclic depsipeptide and isolated *Symploca* sp. The natural products of Largazole showed specific bio-activity with differential growth inhibition (2-10%) of mice cell lines and transformed, non-transformed human cell lines (Bowers et al. 2008).

Veraguamides, cyclic hexadepsipeptides generated from the ocean cyanobacterium *Symploca cf. hydnoides* and collected from the Micronesian island, were cytotoxic against colon adenocarcinoma HT29 and cervical cancer

cell lines HeLa (Salvador et al. 2011). Freshwater cyanobacterial extracts of *Carotinosum* and *N. linckia* showed antiproliferative and cytotoxic effects on the rat Glioma C6 cell line (Karan and Aydin 2018).

Similarly, *A. oryzae* extract suppressed the growth of MCF7 breast cancer cells (Karan and Aydin 2018). Apratoxin A, a cyclic depsipeptide produced from *Lyngbya* spp., has a fatal impact on human cervical carcinoma HeLa cell lines by interfering with the cell cycle (Malve 2016). Peptides were isolated from cyanobacteria *Nostoc* sp. and *Lyngbya* sp. exhibited anticancer activity by inhibiting dissociation of microfilaments and secretory pathways (Malve 2016). *Synechocystis* sp. and *Synechococcus* sp. aqueous extracts showed anticancer activities against HL-60 human leukemia cell lines by activating apoptosis and membrane budding (Martins et al. 2008).

Several reports have been published that photosynthetic pigments also act as anticancer activity. C-phycocyanin (CP) is a photosynthetic pigment that shows anti-tumor activity by suppressing the growth of tumor in a concentration and time-dependent manner. CP exhibited potent anticancer properties in several cancer cell lines, including breast cancer (Li et al. 2010)**,** colon cancer (Wang et al. 2007)**,** and bone marrow cancer (Gardeva et al. 2014); multiple processes are involved, including the production of reactive oxygen species (ROS), programmed cell death, and cell cycle inhibition (Pan et al. 2015; Hao et al. 2021).

The extract of *Arthrospira platensis* containing phycocyanin act as an anti-cancer drug for various tumor cells (Jiang et al. 2017; Braune et al. 2021) found that phycocyanin is a promising source of anticancer agents due to the inhibition of cell-cycle arrest, stimulation of cell apoptosis, autophagy and reduction of ant-proliferating activity. Human prostate cell line LNCaP cured by combined application of C-phycocyanin and 10% topotecan as compared with C-PC treatment and single topotecan. It activates a series of caspases by producing radical oxygen (ROS) that leads to the apoptosis of tumor cells and inhibits toxicity generated by topotecan (Gantar et al. 2012).

1.5 Biosynthesis of bioactive compounds

Cyanobacteria synthesized different groups of natural products and showed different chemical natures. Alkaloids, polyketides, terpenes, fatty acids, and UV-absorbing chemicals are bioactive compounds. Peptide biosynthesis operates into ribosome-independent pathways and is operated by enzymes known as non-ribosomal peptide synthetase (NRP_S), and further peptides are modified during post-translational modification and processing. NRPs are a kind of secondary metabolite found in various microorganisms, including bacteria, cyanobacteria, fungi, and plants (Singh et al. 2019). Non-ribosomal peptides synthetases are multimodular proteins, and it synthesized by known as NRPs genes. Single module domain proteins are also reported, and approximately 3 to 3.5 Kb genetic sequences are required. They are multifunctional multimodular enzymes; that consist of non-ribosomal peptide synthetases (NPSs) and polyketide synthases (PK_S), which are responsible for the biosynthesis of non-ribosomal peptides and polyketides, respectively (Ref. figure 1 & 2).

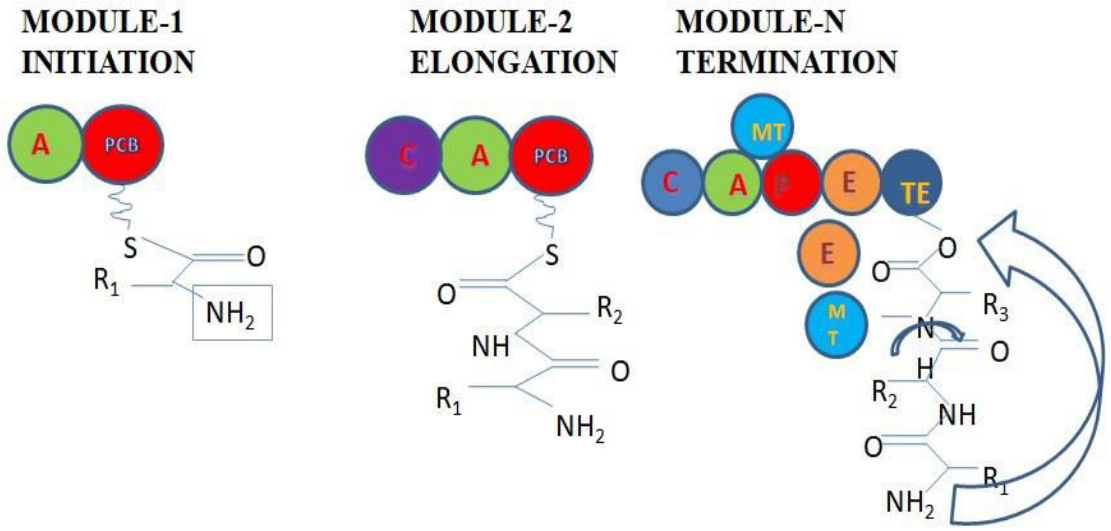

Figure.1. Nonribosomal peptides synthetases (NPSs) consist of different domains; adenylation domain (A), peptidyl carrier domain (PCB), condensation domain (C) thioesterase domain (TE), epimerization domain (E), and methyltransferase (MT) domain. These enzymes catalyzed synthesis of nonribosomal peptides.

Diversity of these bioactive compounds (peptides and polyketides)is maintained by NRPSs (Süssmuth and Mainz 2017). NRPs activated and incorporate amino acids (D and L), hydroxy acids, keto acid, heterocyclic and other functional groups. They contribute structural and chemical diversity of the peptides (McErlean et al. 2019; Kudo et al. 2019). Consequently, NRPSs are extraordinary macromolecular machines that generate various physiologically and therapeutically significant compounds. (Bloudoff and Schmeing 2017).

The several modules of NRPS are responsible for the progressive incorporation of amino acids. The majority of modules are composed of three domains: the adenylation domain (A) (amino acid activation domain), the peptidyl carrier domain (PCB), and the condensation domain (C) (Fig.1) (Koglin and Walsh 2009; Marahiel and Essen 2009). NRPs may add up to 300 proteinogenic and non-proteinogenic substrates, in addition to domain-specific tailoring modifications and amino acid epimerization as substrates (Miller and Gulick 2016). These groups of peptide biosynthetic processes displayed diverse natures and considerable activity. Ribosome-mediated peptides can add only 20 amino acids, and leader and core peptides are an integral part of proteins.

Amino acids are selected and activated by the adenylation domain (Finking and Marahiel 2004; Marahiel and Essen 2009). The peptide carrier protein and condensation domains entail the formation of peptide bonds between two amino acids and the binding to peptidyl carrier proteins. The adenylation and peptidyl carrier protein domains are components of an initiation module. The thioesterase domain catalyzes the production of a macrocycle and the release of molecules (TE) (Finking and Marahiel 2004; Marahiel and Essen 2009). The presence of tailoring domains might increase the number of peptide modifications possible. A few of the tailoring domains are the epimerization domain (E), which converts L- to D-amino acids; the methyltransferase domain (MT), which methylates amino acid residues; and the monooxygenase domains (OX), which adds one hydroxyl group to substrates. (Finking and Marahiel 2004; Marahiel and Essen 2009). Glycosyltransferases are the enzymes responsible for adding sugar units to free hydroxyl groups on polypeptides. (Finking and Marahiel 2004; Welker and Von Döhren 2006)

Similarly, PKS-type I modules must have at least the following domains: acyltransferase (AT), acyl carrier protein (ACP), and ketosynthase (KS). Acyltransferase picked one unit and incorporated it into the peptide malonyl-, methyl-, ethyl-, and propylmalonyl-CoA (Katz 1997). The malonyl-CoA unit is transferred to the acyl carrier protein, and the ketosynthase domain enables the development of a Claisen-condensation link between the

two units. During the last stages of elongation, the thioesterase domain (TE) cleaves and macrocyclizes the product in every PKS domain. It was reported that NRPS and PKS domains are present in the hybrid system and are involved in the secondary metabolites production of cyanobacteria (Wang et al. 2014). A fatty acid part can be found in the chemical structure of a few non-ribosomal peptides and polyketides. Fatty acid synthesis can take two forms; type I, which involves large multifunctional proteins, and type II, which involves working specific proteins (Campbell and Cronan 2001). Type II is more prevalent in bacterial systems and has more conserved or less conserved protein sequences, such as enoyl reductases, Fab fatty acid biosynthesis, acyl-CoA carboxylase, or (ER), respectively. (Campbell and Cronan 2001). In addition, other proteins, including acyl carrier protein (ACP) and biotin carboxyl carrier protein (BCCB), are involved in fatty acid production (Campbell and Cronan 2001).

Fatty acyl-CoA ligases (FACLs) might produce fatty acetaldehyde, an intermediate unit for the derivative of coenzyme A (Trivedi et al. 2004; Arora et al. 2009). The production of lipid molecules is promoted by activated fatty acyladenylates (Arora et al. 2009)

Curacin A is a secondary metabolite formed by the addition of fatty acids by PKSs or the condensation domain of NRPS, which acts as an accepter of a β-hydroxyl fatty acid (Rausch et al. 2007). Surfactin (Arima et al. 1968; Rausch et al. 2007), lichenysin (Horowitz and Griffin 1991), fengycin (Tosato et al. 1997), arthrofactin (Morikawa et al. 1993), polymyxin (Choi et al. 2009), and pelgipeptin (Horowitz and Griffin 1991) are examples of biosynthetic gene clusters.

1.6 Methods for Isolation and Characterization of Bioactive Compounds

A variety of approaches are used to extract valuable secondary metabolites. Extracellular and intracellular metabolites can be extracted simultaneously (extracellular and intracellular metabolites) or sequentially (intercellular metabolites). Both extraction methods start with liquid nitrogen, quenching to freeze the metabolic activity. Organic solvent (butanol, acetone, hexane, chloroform) and a mixture of water and organic solvent in different ratios is generally used for immediate quenching in the simultaneous extractions. Classical extraction methods generally used solid–liquid (SLE) and liquid–liquid (LLE). SLE method Soxhlet is often used, and solutes are extracted from solids or matrices in a liquid solvent.

In contrast, in LLE, both phases are liquid, and the separations of the solutes are based on the distribution coefficient of the solute in the liquid solvent. All these extraction methods, SLE and LLE, need large amounts of solvent and time. The drawback of the methods is their poor reproducibility.

Some other low-caste methods, such as extraction, supercritical fluid extraction (SFE), and pressurized liquid extraction (PLE), are also applied. Solutes are extracted in SCF by employing gases above the critical temperature. Carbon dioxide is most popularly used as a supercritical fluid, and sometimes methanol or ethanol is also used as a co-solvent. Some researchers extracted antibacterial components from *S. platensis* using carbon dioxide and 10% ethanol (co-solvent) (Mendiola et al. 2007). Using a combination of pressurized-liquid and solid-phase extraction (PLE–SPE), Onofrejova et al. extracted bioactive phenols from freshwater and marine algae (Onofrejová et al. 2010).

Several analytical methods are available for detecting and purifying bioactive molecules from the extract of cyanobacterial **(Fig. 2)**.

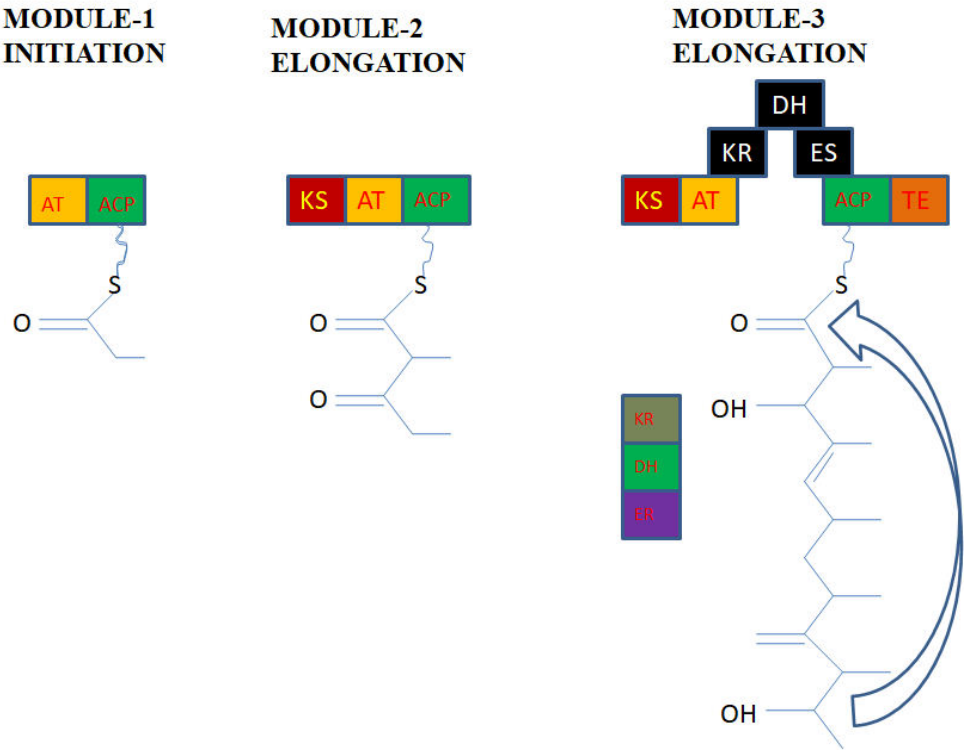

Figure.2. Multifunctional and multimodular polyketides synthases (PKS), consist of different domains (acyltransferase (AT), acyl carrier protein (ACP), ketosynthase (KS), thioesterase domain (TE). These enzymes are involved in biosynthesis of polyketides.

The simplest approach for identifying and separating bioactive compounds is thin layer chromatography (TLC), followed by spectrophotometric analysis. Pelandder et al. separated short cyanobacterial peptides utilizing high-performance TLC plates (HPTLC) (Pelander et al. 2000). Conversely, TLC/HTLC separation is nonspecific and poorly sensitive. The application of high-performance liquid chromatography (HPLC) for detection and characterization has grown considerably. Ultra-performance liquid chromatography (UPLC), a more modern method, is now available, and it might be a better alternative than HPLC. Liquid chromatography is followed by mass spectrometry (LC-MS) to accurately identify a bioactive compound (Harada et al. 2004). The different configurational approaches utilized are atom bombardment (FAB-LC–MS) and electrospray ionization (ESI-LC-MS). Zhang et al. used electrospray ionisation with LC–MS–MS to identify cyanobacterial cyclopeptides (Zhang et al. 2021). Liquid-liquid extraction can be coupled with quadruple time-of-flight tandem mass spectrometry (LC/Q-TOF-MS)**.**

Immunoassay methods are widely used to characterize biomolecules due to their better sensitivity, specificity, and easy operation. Lindner et al. reported that enzyme-linked immunosorbent assays are highly sensitive methods for characterizing cyanobacterial cyclopeptides (Lindner et al. 2004). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is also used to characterize the metabolites. This approach uses a minimal sample size and does not need sample separation or measurement (Welker et al. 2002).

Identification and characterization of intact cyanobacterial cells using MALDI-TOF-MS were reported by (Welker et al. 2002). MALDI-TOF MS is frequently used to identify peptides but may also be used to identify alkaloids. Desorption electrospray ionization mass spectrometry (DESI-MS) is also utilized for chemical profiling, characterization, and quantification of lower molecular weight biomolecules (Bayona et al. 2022). Direct analysis in real-time mass spectrometry (DART-MS) is another approach that may be used for the chemical profiling and characterization of bioactive chemicals. Tripathi et al. used DART-MS to identify the

Nostoc sp.-based chemical components (chemical fingerprinting) (Tripathi et al. 2021). These approaches are useful in identifying and characterizing bioactive molecules.

CONCLUSION

Cyanobacteria are a unique group of photosynthetic autotrophic bacteria, primary producers and distributed worldwide. They provide food to many micro and macro-organisms, and their food habitats differ from heterotrophic bacteria. During the last two decades, they have been recognized as an emerging source of therapeutic bioactive compounds. In contrast to protein biosynthesis, NRPs are large multimodular enzymes with multiple subunits. Secondary metabolites produced by cyanobacteria include alkaloids, polyketides, and non-ribosomal peptides. Non-ribosomal peptides are secondary metabolites synthesized by prokaryotes, especially cyanobacteria and lower eukaryotes; they are diverse in nature, such as pigments, toxins, siderophores and others. Thus, the studies of cyanobacterial-based bioactive compounds are promising endeavour. We have explained several bioactive compounds derived from cyanobacteria and have a broad spectrum of activity, such as antibacterial, antiviral, anticancer and antiprotozoal. Due to simple microbes, cyanobacteria are an excellent option for drug discovery because it requires inorganic nutrient media and is easy to cultivate. Consequently, we advise expanding cyanobacterial drug discovery efforts and enhancing biotechnological and bioprocess engineering for chemical production.

REFERENCES

Arima K, Kakinuma A, Tamura G (1968) Surfactin, a crystalline peptidelipid surfactant produced by Bacillus subtilis: Isolation, characterization and its inhibition of fibrin clot formation. Biochem Biophys Res Commun 31:488–494. https://doi.org/10.1016/0006-291X(68)90503-2

Arora P, Goyal A, Natarajan VT, Rajakumara E, Verma P, Gupta R, Yousuf M, Trivedi OA, Mohanty D, Tyagi A, Sankaranarayanan R, Gokhale RS (2009) Mechanistic and functional insights into fatty acid activation in Mycobacterium tuberculosis. Nat Chem Biol 5:166–173. https://doi.org/10.1038/nchembio.143

Asthana RK, Deepali, Tripathi MK, Srivastava A, Singh AP, Singh SP, Nath G, Srivastava R, Srivastava BS (2009) Isolation and identification of a new antibacterial entity from the Antarctic cyanobacterium Nostoc CCC 537. J Appl Phycol 21:81–88. https://doi.org/10.1007/s10811-008-9328-2

Asthana RK, Srivastava A, Singh AP, Deepali, Singh SP, Nath G, Srivastava R, Srivastava BS (2006) Identification of an antimicrobial entity from the cyanobacterium Fischerella sp. isolated from bark of Azadirachta indica (Neem) tree. J Appl Phycol 18:33–39. https://doi.org/10.1007/s10811-005-9011-9

Bayona LM, de Voogd NJ, Choi YH (2022) Metabolomics on the study of marine organisms. Metabolomics 18:17

Begum SJP, Pratibha S, Rawat JM, Venugopal D, Sahu P, Gowda A, Qureshi KA, Jaremko M (2022) Recent Advances in Green Synthesis , Characterization , and Applications of Bioactive Metallic Nanoparticles. Pharmaceuticals 15:455. https://doi.org/10.3390/ph15040455

Berry MA, Davis TW, Cory RM, Duhaime MB, Johengen TH, Kling GW, Marino JA, Den Uyl PA, Gossiaux D, Dick GJ, Denef VJ (2017) Cyanobacterial harmful algal blooms are a biological disturbance to Western Lake Erie bacterial communities. Environ Microbiol 19:1149–1162. https://doi.org/10.1111/1462-2920.13640

Biondi N, Tredici MR, Taton A, Wilmotte A, Hodgson DA, Losi D, Marinelli F (2008) Cyanobacteria from benthic mats of Antarctic lakes as a source of new bioactivities. J Appl Microbiol 105:105–115. https://doi.org/10.1111/j.1365-2672.2007.03716.x

Bloudoff K, Schmeing TM (2017) Structural and functional aspects of the nonribosomal peptide synthetase condensation domain superfamily: discovery, dissection and diversity. Biochim. Biophys. Acta - Proteins Proteomics 1865:1587–1604

Bowers A, West N, Taunton J, Schreiber SL, Bradner JE, Williams RM (2008) Total Synthesis and Biological Mode of Action of Largazole: A Potent Class I Histone Deacetylase Inhibitor. J Am Chem Soc 130:11219–11222. https://doi.org/10.1021/ja8033763

Braune S, Krüger-Genge A, Kammerer S, Jung F, Küpper JH (2021) Phycocyanin from arthrospira platensis as potential anti-cancer drug: Review of in vitro and in vivo studies. Life 11:1–14

Broniatowska B, Allmendinger A, Kaiser M, Montamat-Sicotte D, Hingley-Wilson S, Lalvani A, Guiry M, Blunden G, Tasdemir D (2011) Antiprotozoal, antitubercular and cytotoxic potential of cyanobacterial (blue-green algal) extracts from Ireland. Nat Prod Commun 6:689–694. https://doi.org/10.1177/1934578x1100600523

Campbell JW, Cronan J (2001) Bacterial fatty acid biosynthesis: Targets for antibacterial drug discovery. Annu. Rev. Microbiol. 55:305–332

Cannell RJP, Kellam SJ, Owsianka AM, Walker JM (1987) Microalgae and Cyanobacteria as a source of glycosidase inhibitors. J Gen Microbiol 133:1701–1705. https://doi.org/10.1099/00221287-133-7-1701

Carmeli S, Moore RE, Patterson GML, Corbett TH, Valeriote FA (1990) Tantazoles: Unusual Cytotoxic Alkaloids from the Blue-Green Alga Scytonema mirabile. J Am Chem Soc 112:8195–8197. https://doi.org/10.1021/ja00178a070

Catassi A, Cesario A, Arzani D, Menichini P, Alama A, Bruzzo C, Imperatori A, Rotolo N, Granone P, Russo P (2006) Characterization of apoptosis induced by marine natural products in non small cell lung cancer A549 cells. Cell Mol Life Sci 63:2377–2386. https://doi.org/10.1007/s00018-006-6264-7

Chirasuwan N, Chaiklahan R, Kittakoop P, Chanasattru W, Ruengjitchatchawalya M, Tanticharoen M, Bunnag B (2009) Anti HSV-1 activity of sulphoquinovosyl diacylglycerol isolated from spirulina platensis. ScienceAsia 35:137–141. https://doi.org/10.2306/scienceasial513-1874.2009.35.137

Choi SK, Park SY, Kim R, Kim S Bin, Lee CH, Kim JF, Park SH (2009) Identification of a polymyxin synthetase gene cluster of Paenibacillus polymyxa and heterologous expression of the gene in Bacillus subtilis. J Bacteriol 191:3350–3358. https://doi.org/10.1128/JB.01728-08

Clardy J, Fischbach MA, Walsh CT (2006) New antibiotics from bacterial natural products. Nat. Biotechnol. 24:1541–1550

Clark BR, Engene N, Teasdale ME, Rowley DC, Matainaho T, Valeriote FA, Gerwick WH (2008) Natural products chemistry and taxonomy of the marine cyanobacterium Blennothrix cantharidosmum. J Nat Prod 71:1530–1537. https://doi.org/10.1021/np800088a

Cowan G (2000) Rickettsial diseases: The typhus group of fevers - A review. Postgrad. Med. J. 76:269–272

De Morais MG, Vaz B da S, De Morais EG, Costa JAV (2015) Biologically Active Metabolites Synthesized by Microalgae. Biomed Res. Int. 2015:1–15

Demay J, Bernard C, Reinhardt A, Marie B (2019) Natural products from cyanobacteria: Focus on beneficial activities. Mar. Drugs 17:320

Díez B, Bergman B, El-Shehawy R (2008) Marine diazotrophic cyanobacteria: Out of the blue. Plant Biotechnol. 25:221–225

Fan J, Ho L, Hobson P, Brookes J (2013) Evaluating the effectiveness of copper sulphate, chlorine, potassium permanganate, hydrogen peroxide and ozone on cyanobacterial cell integrity. Water Res 47:5153–5164. https://doi.org/10.1016/j.watres.2013.05.057

Finking R, Marahiel MA (2004) Biosynthesis of nonribosomal peptides. Annu. Rev. Microbiol. 58:453–488

Fish SA, Codd GA (1994) Bioactive compound production by thermophilic and thermotolerant cyanobacteria (blue-green algae). World J Microbiol Biotechnol 10:338–341 . https://doi.org/10.1007/BF00414875

Gademann K, Bethuel Y, Locher HH, Hubschwerlen C (2007) Biomimetic total synthesis and antimicrobial evaluation of anachelin H. J Org Chem 72:8361–8370. https://doi.org/10.1021/jo701402b

Gantar M, Dhandayuthapani S, Rathinavelu A (2012) Phycocyanin induces apoptosis and enhances the effect of topotecan on prostate cell line LNCaP. J Med Food 15:1091–1095. https://doi.org/10.1089/jmf.2012.0123

Gardeva EG, Toshkova RA, Yossifova LS, Minkova K, Ivanova NY, Gigova LG (2014) Antitumor activity of C-phycocyanin from Arthronema africanum (Cyanophyceae). Brazilian Arch Biol Technol 57:675–684. https://doi.org/10.1590/S1516-89132014005000018

Gayakwad S, Dixit A, Shirolkar A, Warkad S, Devlae A, Murthy SN, Pawar S (2015) Phytochemical Characterization and Cells Based Analysis of Bioactive Components of Nothapodytes nimmoniana (J. Graham)

Ghasemi Y, Tabatabaei Yazdi M, Shafiee A, Amini M, Shokravi S, Zarrini G (2004) Parsiguine, a novel antimicrobial substance from Fischerella ambigua. Pharm Biol 42:318–322. https://doi.org/10.1080/13880200490511918

Gupta DK, Kaur P, Leong ST, Tan LT, Prinsep MR, Chu JJH (2014) Anti-Chikungunya viral activities of aplysiatoxin-related compounds from the marine cyanobacterium Trichodesmium erythraeum. Mar Drugs 12:115–127. https://doi.org/10.3390/md12010115

Gustafson KR, Cardellina JH, Fuller RW, Weislow OS, Kiser RF, Snader KM, Patterson GML, Boyd MR (1989) AIDS-antiviral sulfolipids from cyanobacteria (Blue-Green Algae). J Natl Cancer Inst 81:1254–1258. https://doi.org/10.1093/jnci/81.16.1254

Hagmann L, Jüttner F (1996) Fischerellin A, a novel photosystem-II-inhibiting allelochemical of the cyanobacterium Fischerella muscicola with antifungal and herbicidal activity. Tetrahedron Lett 37:6539–6542. https://doi.org/10.1016/0040-4039(96)01445-1

Han B, Goeger D, Maier CS, Gerwick WH (2005) The wewakpeptins, cyclic depsipeptides from a Papua new guinea collection of the marine cyanobacterium Lyngbya semiplena. J Org Chem 70:3133–3139. https://doi.org/10.1021/jo0478858

Hao A, Haraguchi T, Kuba T, Kai H, Lin Y, Iseri Y (2021) Effect of the microorganism-adherent carrier for Nitzschia palea to control the cyanobacterial blooms. Ecol Eng 159:106127. https://doi.org/10.1016/j.ecoleng.2020.106127

Harada KI, Tomita K, Fujii K, Masuda K, Mikami Y, Yazawa K, Komaki H (2004) Isolation and structural characterization of siderophores, madurastatins, produced by a pathogenic Actinomadura madurae. J Antibiot (Tokyo) 57:125–135. https://doi.org/10.7164/antibiotics.57.125

Harvey AL, Edrada-Ebel R, Quinn RJ (2015) The re-emergence of natural products for drug discovery in the genomics era. Nat. Rev. Drug Discov. 14:111–129

Hayashi K, Hayashi T, Ujita K, Takaishi Y (1996) Characterization of antiviral activity of a sesquiterpene, triptofordin C-2. J Antimicrob Chemother 37:759–768. https://doi.org/10.1093/jac/37.4.759

Hood P, Khan E (eds) (2020) Understanding Pharmacology in Nursing Practice. Springer International Publishing, Cham

Horowitz S, Griffin WM (1991) Structural analysis of Bacillus licheniformis 86 surfactant. J Ind Microbiol 7:45–52. https://doi.org/10.1007/BF01575602

Jaki B, Orjala J, Heilmann J, Linden A, Vogler B, Sticher O (2000) Novel extracellular diterpenoids with

biological activity from the cyanobacterium Nostoc commune. J Nat Prod 63:339–343. https://doi.org/10.1021/np9903090

Jiang L, Wang Y, Yin Q, Liu G, Liu H, Huang Y, Li B (2017) Phycocyanin: A potential drug for cancer treatment. J Cancer 8:3416–3429. https://doi.org/10.7150/jca.21058

Jordan MA, Wilson L (1998) Microtubules and actin filaments: Dynamic targets for cancer chemotherapy. Curr Opin Cell Biol 10:123–130. https://doi.org/10.1016/S0955-0674(98)80095-1

Kalemkerian GP, Ou X, Adil MR, Rosati R, Khoulani MM, Madan SK, Pettit GR (1999) Activity of dolastatin 10 against small-cell lung cancer in vitro and in vivo: Induction of apoptosis and bcl-2 modification. Cancer Chemother Pharmacol 43:507–515. https://doi.org/10.1007/s002800050931

Kanekiyo K, Hayashi K, Takenaka H, Lee JB, Hayashi T (2007) Anti-herpes simplex virus target of an acidic polysaccharide, nostoflan, from the edible blue-green alga Nostoc flagelliforme. Biol Pharm Bull 30:1573–1575. https://doi.org/10.1248/bpb.30.1573

Kanekiyo K, Lee JB, 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 68:1037–1041. https://doi.org/10.1021/np050056c

Karan T, Aydin A (2018) Anticancer potential and cytotoxic effect of some freshwater cyanobacteria. Trop J Pharm Res 17:2183–2188. https://doi.org/10.4314/tjpr.v17i11.11

Karchmer AW (2004) Increased antibiotic resistance in respiratory tract pathogens: PROTEKT US - An update. In: Clinical Infectious Diseases. pp S142–S150

Kashiwagi T, Du F, Douglas JF, Winey KI, Harris RH, Shields JR (2005) Nanoparticle networks reduce the flammability of polymer nanocomposites. Nat Mater 4:928–933. https://doi.org/10.1038/nmat1502

Katz BA (1997) Structural and mechanistic determinants of affinity and specificity of ligands discovered or engineered by phage display. Annu. Rev. Biophys. Biomol. Struct. 26:27–45

Kellam SJ, Walker JM (1989) Antibacterial activity from marine microalgae in laboratory culture. Br. Phycol. J. 24:191–194

Koglin A, Walsh CT (2009) Structural insights into nonribosomal peptide enzymatic assembly lines. Nat Prod Rep 26:987–1000. https://doi.org/10.1039/b904543k

Kudo H, Hayashi Y, Arai M (2019) Improving hydrocarbon production by engineering cyanobacterial acyl-(acyl carrier protein) reductase. Biotechnol Biofuels 12:291. https://doi.org/10.1186/s13068-019-1623-4

Li Y, Han D, Hu G, Sommerfeld M, Hu Q (2010) Inhibition of starch synthesis results in overproduction of lipids in Chlamydomonas reinhardtii. Biotechnol Bioeng 107:258–268. https://doi.org/10.1002/bit.22807

Lindner P, Molz R, Yacoub-George E, Dürkop A, Wolf H (2004) Development of a highly sensitive inhibition immunoassay for microcystin-LR. Anal Chim Acta 521:37–44. https://doi.org/10.1016/j.aca.2004.05.059

Linington RG, Edwards DJ, Shuman CF, McPhail KL, Matainaho T, Gerwick WH (2008) Symplocamide A, a potent cytotoxin and chymotrypsin inhibitor from the marine cyanobacterium Symploca sp. J Nat Prod 71:22–27 . https://doi.org/10.1021/np070280x

Luesch H, Moore RE, Paul VJ, Mooberry SL, Corbett TH (2001) Isolation of dolastatin 10 from the marine cyanobacterium Symploca species VP642 and total stereochemistry and biological evaluation of its analogue symplostatin 1. J Nat Prod 64:907–910. https://doi.org/10.1021/np010049y

Malve H (2016) Exploring the ocean for new drug developments: Marine pharmacology. J. Pharm. Bioallied Sci. 8:83–91

Mansour H, Shoman S, Kdodier M (2011) Antiviral effect of edaphic cyanophytes on rabies and herpes-1 viruses. Acta Biol Hung 62:194–203. https://doi.org/10.1556/ABiol.62.2011.2.9

Marahiel MA, Essen LO (2009) Chapter 13 Nonribosomal Peptide Synthetases. Mechanistic and Structural Aspects of Essential Domains. Methods Enzymol. 458:337–351

Martins RF, Ramos MF, Herfindal L, Sousa JA, Skærven K, Vasconcelos VM (2008) Antimicrobial and cytotoxic assessment of marine cyanobacteria - Synechocystis and Synechococcus. Mar Drugs 6:1–11. https://doi.org/10.3390/md6010001

Matthew S, Schupp PJ, Luesch H (2008) Apratoxin E, a cytotoxic peptolide from a guamanian collection of the marine cyanobacterium Lyngbya bouillonii. J Nat Prod 71:1113–1116. https://doi.org/10.1021/np700717s

Mayer AMS, Murphy J, MacAdam D, Osterbauer C, Baseer I, Hall ML, Feher D, Williams P (2016) Classical and alternative activation of cyanobacterium Oscillatoria sp. lipopolysaccharide-treated rat microglia in vitro. Toxicol Sci 149:484–495. https://doi.org/10.1093/toxsci/kfv251

McErlean M, Overbay J, Van Lanen S (2019) Refining and expanding nonribosomal peptide synthetase function and mechanism. J. Ind. Microbiol. Biotechnol. 46:493–513

McPhail KL, Correa J, Linington RG, González J, Ortega-Barría E, Capson TL, Gerwick WH (2007) Antimalarial linear lipopeptides from a panamanian strain of the marine cyanobacterium Lyngbya majuscula. J Nat Prod 70:984–988. https://doi.org/10.1021/np0700772

Meeks JC, Campbell EL, Summers ML, Wong FC (2002) Cellular differentiation in the cyanobacterium Nostoc punctiforme. Arch. Microbiol. 178:395–403

Mendiola JA, Jaime L, Santoyo S, Reglero G, Cifuentes A, Ibañez E, Señoráns FJ (2007) Screening of functional compounds in supercritical fluid extracts from Spirulina platensis. Food Chem 102:1357–1367. https://doi.org/10.1016/j.foodchem.2006.06.068

Miller BR, Gulick AM (2016) Structural biology of nonribosomal peptide synthetases. In: Methods in Molecular Biology. Humana Press Inc., pp 3–29

Mo S, Krunic A, Chlipala G, Orjala J (2009) Antimicrobial ambiguine isonitriles from the cyanobacterium Fischerella ambigua. J Nat Prod 72:894–899. https://doi.org/10.1021/np800751j

Morikawa M, Daido H, Takao T, Murata S, Shimonishi Y, Imanaka T (1993) A new lipopeptide biosurfactant produced by Arthrobacter sp. strain MIS38. J Bacteriol 175:6459–6466. https://doi.org/10.1128/jb.175.20.6459-6466.1993

Musale AS, Raja G, Kumar K, Sapre A, Dasgupta S (2020) Marine Algae as a Natural Source for Antiviral Compounds. AIJR Prepr 38:1–6. https://doi.org/https://doi.org/10.21467/preprints.38

Nagle DG, Geralds RS, Yoo HD, Gerwick WH, Kim TS, Nambu M, White JD (1995) Absolute configuration of curacin A, a novel antimitotic agent from the tropical marine cyanobacterium Lyngbya majuscula. Tetrahedron Lett 36:1189–1192. https://doi.org/10.1016/0040-4039(95)00030-G

Newman DJ, Cragg GM (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. J. Nat. Prod. 75:311–335

Oftedal L, Selheim F, Wahlsten M, Sivonen K, Døskeland SO, Herfindal L (2010) Marine benthic cyanobacteria contain apoptosis-inducing activity synergizing with daunorubicin to kill leukemia cells, but not cardiomyocytes. Mar Drugs 8:2659–2672. https://doi.org/10.3390/md8102659

Onofrejová L, Vašíčková J, Klejdus B, Stratil P, Mišurcová L, Kráčmar S, Kopecký J, Vacek J (2010) Bioactive phenols in algae: The application of pressurized-liquid and solid-phase extraction techniques. J Pharm Biomed

Anal 51:464–470. https://doi.org/10.1016/j.jpba.2009.03.027

Pan H, Jia R, Zhang L, Xu S, Wu Q, Song X, Zhang H, Ge S, Leon Xu X, Fan X (2015) BAP1 regulates cell cycle progression through E2F1 target genes and mediates transcriptional silencing via H2A monoubiquitination in uveal melanoma cells. Int J Biochem Cell Biol 60:176–184. https://doi.org/10.1016/j.biocel.2015.01.001

Paterson DL (2006) The epidemiological profile of infections with multidrug-resistant Pseudomonas aeruginosa and Acinetobacter species. In: Clinical Infectious Diseases. pp 43–51

Pelander A, Ojanperä I, Lahti K, Niinivaara K, Vuori E (2000) Visual detection of cyanobacterial hepatotoxins by thin-layer chromatography and application to water analysis. Water Res 34:2643–2652. https://doi.org/10.1016/S0043-1354(00)00006-3

Pérez Gutiérrez RM, Martínez Flores A, Vargas Solís R, Carmona Jimenez J (2008) Two new antibacterial norabietane diterpenoids from cyanobacteria, Microcoleous lacustris. J Nat Med 62:328–331. https://doi.org/10.1007/s11418-008-0238-z

Qureshi KA, Bholay AD, Rai PK, Mohammed HA, Khan RA, Azam F, Jaremko M, Emwas AH, Stefanowicz P, Waliczek M, Kijewska M, Ragab EA, Rehan M, Elhassan GO, Anwar MJ, Prajapati DK (2021a) Isolation, characterization, anti-MRSA evaluation, and in-silico multi-target anti-microbial validations of actinomycin X2 and actinomycin D produced by novel Streptomyces smyrnaeus UKAQ_23. Sci Rep 11:14539. https://doi.org/10.1038/s41598-021-93285-7

Qureshi KA, Imtiaz M, Nasr I Al, Koko WS, Khan TA, Jaremko M, Mahmood S, Fatmi MQ (2022) Antiprotozoal Activity of Thymoquinone (2-Isopropyl-5-methyl-1,4-benzoquinone) for the Treatment of Leishmania major-Induced Leishmaniasis: In Silico and In Vitro Studies. Antibiotics 11:1206. https://doi.org/10.3390/ANTIBIOTICS11091206

Qureshi KA, Nasr I Al, Koko WS, Khan TA, Fatmi MQ, Imtiaz M, Khan RA, Mohammed HA, Jaremko M, Emwas AH, Azam F, Bholay AD, Elhassan GO, Prajapati DK (2021b) In vitro and in silico approaches for the antileishmanial activity evaluations of actinomycins isolated from novel Streptomyces smyrnaeus strain UKAQ_23. Antibiotics 10:887. https://doi.org/10.3390/antibiotics10080887

Ramakrishna A, Ravishankar GA (2011) Influence of abiotic stress signals on secondary metabolites in plants. Plant Signal. Behav. 6:1720–1731

Rausch C, Hoof I, Weber T, Wohlleben W, Huson DH (2007) Phylogenetic analysis of condensation domains in NRPS sheds light on their functional evolution. BMC Evol Biol 7:1–15. https://doi.org/10.1186/1471-2148-7-78

Rechter S, König T, Auerochs S, Thulke S, Walter H, Dörnenburg H, Walter C, Marschall M (2006) Antiviral activity of Arthrospira-derived spirulan-like substances. Antiviral Res 72:197–206. https://doi.org/10.1016/j.antiviral.2006.06.004

Reichelt JL, Borowitzka MA (1984) Antimicrobial activity from marine algae: Results of a large-scale screening programme. In: Eleventh International Seaweed Symposium. Springer Netherlands, Dordrecht, pp 158–168

Reynolds R, Potz N, Colman M, Williams A, Livermore D, MacGowan A, Allen M, Brown DFJ, Deaney N, Harding I, Reed V, Thomson C, Thorne G, White A, Wiltshire R, Wise R, George R (2004) Antimicrobial susceptibility of the pathogens of bacteraemia in the UK and Ireland 2001-2002: The BSAC bacteraemia resistance surveillance programme. J Antimicrob Chemother 53:1018–1032. https://doi.org/10.1093/jac/dkh232

Rickards RW, Rothschild JM, Willis AC, De Chazal NM, Kirk J, Kirk K, Saliba KJ, Smith GD (1999) Calothrixins A and B, novel pentacyclic metabolites from Calothrix cyanobacteria with potent activity against malaria parasites and human cancer cells. Tetrahedron 55:13513–13520. https://doi.org/10.1016/S0040-4020(99)00833-9

Rojas V, Rivas L, Cárdenas C, Guzmán F (2020) Cyanobacteria and eukaryotic microalgae as emerging sources of antibacterial peptides. Molecules 25:5804

Sainis I, Fokas D, Vareli K, Tzakos AG, Kounnis V, Briasoulis E (2010) Cyanobacterial cyclopeptides as lead compounds to novel targeted cancer drugs. Mar. Drugs 8:629–657

Salvador LA, Biggs JS, Paul VJ, Luesch H (2011) Veraguamides A-G, cyclic hexadepsipeptides from a dolastatin 16-producing cyanobacterium Symploca cf. hydnoides from Guam. J Nat Prod 74:917–927 . https://doi.org/10.1021/np200076t

Selim MSM, Abdelhamid SA, Mohamed SS (2021) Secondary metabolites and biodiversity of actinomycetes. J. Genet. Eng. Biotechnol. 19:72

Simmons TL, Engene N, Ureña LD, Romero LI, Ortega-Barría E, Gerwick L, Gerwick WH (2008) Viridamides A and B, lipodepsipeptides with antiprotozoal activity from the marine cyanobacterium Oscillatoria nigro-viridis. J Nat Prod 71:1544–1550. https://doi.org/10.1021/np800110e

Singh B, Singh JP, Shevkani K, Singh N, Kaur A (2017) Bioactive constituents in pulses and their health benefits. J. Food Sci. Technol. 54:858–870

Singh H, Tomar S, Qureshi KA, Jaremko M, Rai PK (2022) Recent Advances in Biomass Pretreatment Technologies for Biohydrogen Production. Energies 15:1–22. https://doi.org/10.3390/en15030999

Singh MK, Rai PK, Rai A, Singh S, Singh JS (2019) Poly-β-hydroxybutyrate production by the cyanobacterium scytonema geitleri bharadwaja under varying environmental conditions. Biomolecules 9:198 . https://doi.org/10.3390/biom9050198

Singh N, Mishra BB, Bajpai S, Singh RK, Tiwari VK (2014) Natural product based leads to fight against leishmaniasis. Bioorganic Med. Chem. 22:18–45

Singh S, Kate BN, Banecjee UC (2005) Bioactive compounds from cyanobacteria and microalgae: An overview. Crit. Rev. Biotechnol. 25:73–95

Smith CD, Zhang X, Mooberry SL, Patterson GML, Moore RE (1994) Cryptophycin: A New Antimicrotubule Agent Active against Drug-resistant Cells. Cancer Res 54:3779–3784. https://doi.org/3779-3784

Starr MP, Moran F (1962) Eliminative split of pectic substances by phytopathogenic soft-rot bacteria. Science (80-) 135:920–921. https://doi.org/10.1126/science.135.3507.920

Süssmuth RD, Mainz A (2017) Nonribosomal Peptide Synthesis—Principles and Prospects. Angew. Chemie - Int. Ed. 56:3770–3821

Sytar O, Smetanska I (2022) Special Issue "Bioactive Compounds from Natural Sources (2020, 2021)." Molecules 27:1929

Tidgewell K, Engene N, Byrum T, Media J, Doi T, Valeriote FA, Gerwick WH (2010) Evolved diversification of a modular natural product pathway: Apratoxins F and G, two cytotoxic cyclic depsipeptides from a palmyra collection of Lyngbya bouillonii. ChemBioChem 11:1458–1466. https://doi.org/10.1002/cbic.201000070

Tosato V, Albertini AM, Zotti M, Sonda S, Bruschi C V. (1997) Sequence completion, identification and definition of the fengycin operon in Bacillus subtilis 168. Microbiology 143:3443–3450. https://doi.org/10.1099/00221287-143-11-3443

Tripathi AH, Negi N, Gahtori R, Kumari A, Joshi P, Tewari LM, Joshi Y, Bajpai R, Upreti DK, Upadhyay SK (2021) A Review of Anti-Cancer and Related Properties of Lichen-Extracts and Metabolites. Anticancer Agents Med Chem 22:115–142. https://doi.org/10.2174/1871520621666210322094647

Trivedi OA, Arora P, Sridharan V, Tickoo R, Mohanty D, Gokhale RS (2004) Enzymic activation and transfer of fatty acids as acyl-adenylates in mycobacteria. Nature 428:441–445. https://doi.org/10.1038/nature02384

Wang H, Fewer DP, Holm L, Rouhiainen L, Sivonen K (2014) Atlas of nonribosomal peptide and polyketide biosynthetic pathways reveals common occurrence of nonmodular enzymes. Proc Natl Acad Sci U S A 111:9259–9264. https://doi.org/10.1073/pnas.1401734111

Wang W, Zhao Y, Rayburn ER, Hill DL, Wang H, Zhang R (2007) In vitro anti-cancer activity and structure-activity relationships of natural products isolated from fruits of Panax ginseng. Cancer Chemother Pharmacol 59:589–601. https://doi.org/10.1007/s00280-006-0300-z

Ward DM, Castenholz RW, Miller SR (2012) Cyanobacteria in geothermal habitats. In: Ecology of Cyanobacteria II: Their Diversity in Space and Time. Springer Netherlands, pp 39–63

Welker M, Fastner J, Erhard M, Von Döhren H (2002) Applications of MALDI-TOF MS analysis in cyanotoxin research. Environ Toxicol 17:367–374. https://doi.org/10.1002/tox.10073

Welker M, Von Döhren H (2006) Cyanobacterial peptides - Nature's own combinatorial biosynthesis. FEMS Microbiol. Rev. 30:530–563

Whitton BA, Potts M (2012) Introduction to the cyanobacteria. Ecol. Cyanobacteria II Their Divers. Sp. Time 9789400738:1–13

Yadav RK, Ramteke PW, Tripathi K, Varghese E, Abraham G (2022) Salinity Induced Alterations in the Growth and Cellular Ion Content of Azolla caroliniana and Azolla microphylla. J Plant Growth Regul. https://doi.org/10.1007/s00344-022-10594-5

Yakoot M, Salem A (2012) Spirulina platensis versus silymarin in the treatment of chronic hepatitis C virus infection. A pilot randomized, comparative clinical trial. BMC Gastroenterol 12:32. https://doi.org/10.1186/1471-230X-12-32

Yang F, Bewley CA, Louis JM, Gustafson KR, Boyd MR, Gronenborn AM, Clore GM, Wlodawer A (1999) Crystal structure of cyanovirin-N, a potent HIV-inactivating protein, shows unexpected domain swapping. J Mol Biol 288:403–412. https://doi.org/10.1006/jmbi.1999.2693

Yang L, Yang C, Li C, Zhao Q, Liu L, Fang X, Chen XY (2016) Recent advances in biosynthesis of bioactive compounds in traditional Chinese medicinal plants. Sci. Bull. 61:3–17

Zainuddin EN, Mundt S, Wegner U, Mentel R (2002) Cyanobacteria a potential source of antiviral substances against influenza virus. Med Microbiol Immunol 191:181–182. https://doi.org/10.1007/s00430-002-0142-1

Zhang JN, Xia YX, Zhang HJ (2021) Natural cyclopeptides as anticancer agents in the last 20 years. Int. J. Mol. Sci. 22

Zheng W, Chen C, Cheng Q, Wang Y, Chu C (2006) Oral administration of exopolysaccharide from Aphanothece halophytica (Chroococcales) significantly inhibits influenza virus (H1N1)-induced pneumonia in mice. Int Immunopharmacol 6:1093–1099. https://doi.org/10.1016/j.intimp.2006.01.020