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REVIEW

Phycochemistry and bioactivity of cyanobacterial secondary metabolites

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Abstract

Microbes are a huge contributor to people's health around the world since they produce a lot of beneficial secondary metabolites. Cyanobacteria are photosynthetic prokaryotic bacteria cosmopolitan in nature. Adaptability of cyanobacteria to wide spectrum of environment can be contributed to the production of various secondary metabolites which are also therapeutic in nature. As a result, they are a good option for the development of medicinal molecules. These metabolites could be interesting COVID-19 therapeutic options because the majority of these compounds have demonstrated substantial pharmacological actions, such as neurotoxicity, cytotoxicity, and antiviral activity against HCMV, HSV-1, HHV-6, and HIV-1. They have been reported to produce a single metabolite active against wide spectrum of microbes like *Fischerella ambigua* produces ambigols active against bacteria, fungi and protozoa. Similarly, *Moorea producens* produces malygomides O and P, majusculamide C and somocystinamide which are active against bacteria, fungi and tumour cells, respectively. In addition to the above, *Moorea* sp. produce apratoxin A and dolastatin 15 possessing anti cancerous activity but unfortunately till date only brentuximab vedotin (trade name Adcetris), a medication derived from marine peptides, for the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma has been approved by FDA. However, several publications have effectively described and categorised cyanobacterial medicines based on their biological action. In present review, an effort is made to categorize cyanobacterial metabolites on the basis of their phycochemistry. The goal of this review is to categorise cyanobacterial metabolites based on their chemical functional group, which has yet to be described.

Keywords Cyanobacteria · Functional groups · Secondary metabolites · COVID-19 · Antimicrobial

Introduction

Microbes are the prodigious contributors to the health of people worldwide as they serve as a prolific source of bioactive secondary metabolites. The microbial drug era started from the discovery of penicillin, discovered by Alexander Fleming. However various evidences witnessed that exposure to antibiotics is not confined to modern era but also existed during ancient era, knowledge regarding use of microbial drugs in ancient era is lacking. For example dating back to 350–550 CE from ancient Sudanese Nabia, tetracycline was found in human skeletal remains in trace amount [1, 2]. Similarly Cook et al.,1989 found antibiotic traces during histological analysis of femoral midshaft samples of late Roman period skeletons from Egypt [3].

Paul Ehrlich and Alexander Fleming did the pioneer work in utilizing microbes for drug production in 1929. Ehrlich's systematic screening program is considered as a milestone in drug search approaches. These discoveries led to initiation of a new era in medicine "The Golden Age of Antibiotics" and since then production of some of the products of pharmaceutical value started for example, antibacterial agents such as penicillins (from *Penicillium* species), immunosuppressive agents such as cyclosporins (from *Trichoderma* sps.) antihelmintics and antiparasitic

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drugs such as the ivermectins (from *Streptomyces* sps.) [1]. Thus it can be concluded that these microbial secondary metabolites can serve as successful source of potential drug leads. The number of natural compounds discovered is more than 1 million. Among these natural compounds 50–60% is contributed by plant secondary metabolites such as alkaloids, flavonoids, terpenoids, steroids, carbohydrate etc. whereas 5% is contributed by microbial secondary metabolites [2].

Moreover, major work in identifying microbial drugs is restricted to chemoheterotrophs. Various other groups need attention so as to explore their potential as source of drug. Cyanobacteria, a diverse group of prokaryotic organism are capable of growing under diverse nutrient conditions, photoautotrophically, photoheterotrophically or chemoheterotrophically. Additionally, they are acquiescent to controlled fermenter studies. Thus above mentioned properties qualify them as a novel source of bioactive compounds and emerging as hot resource for drug search.

Besides, limited effective life span of antibiotics and public awareness toward overprescription and misuse of antibiotics are some other reasons that are drawing attention of clinical microbiologist towards cyanobacterial antimicrobial compounds. Further their survival in extreme environments, such as soda lakes (*Spirulina*, *Cyanospira*), cold and dry polar deserts (*Chroococcidiopsis*) and thermal springs (*Synechococcus*) requires exclusive metabolites that are not present in either higher plants or other microorganism. In addition, another advantage of cyanobacteria as a microbial source for drug discovery is reflected in terms of their economical cultivation as compared to other microorganisms due to their requirement of simple inorganic nutrients for growth.

The non-ribosomal polypeptide (NRP) or hybrid polyketide-NRP biosynthetic pathways can create cyanobacterial metabolites, which exhibit fascinating and diverse biological activity. Their structural types include significant subgroups of naturally occurring substances with therapeutic properties, such as the antibiotic vancomycin, the immunosuppressant cyclosporine, the chemotherapeutic medication bleomycin, and the histone deacetylase inhibitors largazole and santacruzamate A [4–6]. Various techniques are employed for extraction, isolation and purification of these cyanobacterial bioactive metabolites. Interestingly some of these have efficaciously reached to phase II and phase III of clinical trials.

Although various reviews have nicely summarized the cyanobacterial drugs and classified them on the basis of their biological activity. In present review, an effort is made to categorize cyanobacterial compounds on the basis of their chemical functional group.

Major functional groups of antimicrobial compounds from cyanobacteria

Figure 1 represents a flow chart portraying secondary metabolites from cyanobacteria which have been further described below.

Terpenes & terpenoids

Terpenes have general chemical structure $C_{10}H_{16}$, and they occur as diterpenes, triterpenes, and tetraterpenes (C_{20}, C_{30}, and C_{40}), as well as hemiterpenes (C_5) and sesquiterpenes (C_{15}). When the compounds contain additional elements, usually oxygen, they are termed terpenoids. *Nostoc commune* produces an antimicrobial compound noscomin [7], a diterpenoid [8] and is active against *Bacillus cereus, Staphylococcus epidermidis*, and *Escherichia coli*, when compared against standard drug. Scytoscalarol [9] and cybastacines A and B [10] are sesquiterpenes bearing a guanidinium or a guanidino group and were isolated from *Scytonema* and *Nostoc*, respectively.

Alkaloids

Alkaloids are nitrogen molecules that are heterocyclic. Many alkaloids have a well-defined pharmacological profile and are mostly employed in clinical treatments, ranging from analgesics to chemotherapeutics. Alkaloids stand out from all other varieties of natural substances by having a huge structural diversity and no predictable distribution [11]. Morphine, discovered in 1805 from the opium plant *Papaver somniferum*, was the first medically valuable alkaloid; the term morphine originates from the Greek Morpheus,

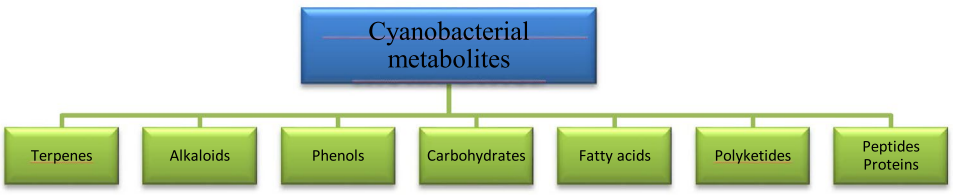


Fig. 1 Flow chart showing cyanobacterial metabolites

God of sleep [12]. Hapalindoles, an indolealkoid produced by *Hapalosiphon fontinalis* [13] exhibit antibacterial antifungal properties. Hapalindole-type alkaloids, ambiguine isonitriles, exhibiting fungicidal activity, are produced by cyanobacterial species *Fischerella ambigua*, *Hapalosiphon hibermicus* and *Westiellopsis prolific* [14]. *Fischerella muscicola*, a terrestrial cyanobacterium, has been shown to produce fischerindole L, an antifungal molecule that is chemically linked to hapalindoles [15]. Nagatsu et al., 1995 [16] reported the production of antibacterial muscoride A, an oxazole peptide alkoid produced from *Nostoc muscorum.* Apart from the above mentioned compound, an alkaloid isolate, nostocarboline, isolated from *Nostoc sp*. found to be active against *Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani* and *Plasmodium falciparum* [17]. Nostocarboline is also a powerful cholinesterase inhibitor, an enzyme that is used to treat Alzheimer's disease [18]. The antifungal compounds tjipanazoles, which are chemically indolocarbazoles, have been isolated from *Tolypothrix tjipanasensis* [19]. *Scytonema mirabile* produces didehydromirabazole which possess antibiotic and cytotoxic activity [20]. *Cylindrospermum licheniforme* and *Cylindrospermopsis raciborskii* produces alkaloids cylindrocyclophane and cylindrospermopsin which are anticancerous and cytotoxic in nature, repectively [21, 22]. Moreover, cylindrospermopsin exhibited promising inhibitory potential against the SARS-CoV-2 M^{PRO} (main protease) [23]. Moderate antibacterial activity has been showed by *Nostoc* sp. CAVN 10 against *Staphylococcus aureus* by the production of paracyclophane called carbamidocyclophane [24]. *Caldora penicillata* produce laucysteinamide A, a new hybrid thiazoline-containing alkaloid that was a monomeric homologue of the disulfide-bonded dimeric molecule somocystinamide A. Human non-small cell lung cancer H-460 cells were moderately cytotoxic by this substance [25]. Carriebowlinol, also known as 5-hydroxy-4-(chloromethyl)-5,6,7,8-tetrahydroquinoline, was discovered in an extensive cyanobacterial mat that was recovered from the coral reef at Carrie Bow Cay in Belize. *Dendryphiella salina, Lindra thalassiae*, and *Fusarium* sp. were all susceptible to carriebowlinol's potent anti-fungal effects. Additionally, this substance showed strong anti-bacterial activity against *Vibrio* sp. [26].

Carbohydrates

Carbohydrates has been identified as another source of antimicrobial compound. *Nostoc flagelliforme* is known to produce nostoflan, an antiviral acidic polysaccharide, having virucidal activity against HSV-1, HSV-2, human cytomegalovirus and influenza A virus [27]. Apart from nostoflan, Calcium spirulan (Ca-SP), a natural sulphated polysaccharide, from *Spirulina platensi*s, which selectively inhibits the penetration of virus into host cells has been reported to show broad range spectrum activity against various enveloped viruses, such as HIV-1, HSV-1, measles virus, mumps virus, influenza A virus and human cytomegalo virus [28]. Polysaccharides are thought to be helpful in treating human coronavirus infections because they have potent antifibrotic effects in the pulmonary tissues. It was shown that the polysaccharides generated from various *Spirulina* species, particularly *Spirulina platensis*, had unique antiviral efficacy against various enveloped viruses. In comparison to the industry standard dextran sulphate, Hayashi assessed the antiviral potential of calcium-spirulan produced from *Spirulina platensis* against HIV-1 and HSV-1. After 24 h of calcium-spirulan treatment, serum samples from the mice models demonstrated persistent antiviral action; nevertheless, their involvement in COVID-19 (SARS-CoV2 infections) is still limited [29, 30].

Phenolics and polyphenols

A single substituted phenolic ring makes up some of the most basic bioactive phytochemicals. In Cyanobacteria, *Phormidium ectocarpii* produces heirridin (2,4-dimethoxy-6-heptadecyl-phenol) which has been reported to possess antiplasmodial and antibiotic activity [31].

Fatty acid

The presence of an amide bond in a fatty acid chain and, in some situations, the incorporation of halogen atoms makes fatty acid amides one of the usual lipophilic class of chemicals. Omega-3 fatty acids, like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in abundance in cyanobacteria are known to prevent inflammatory cardiovascular illnesses [32]. Antibacterial compounds identified from the marine cyanobacterium *Lyngbya majuscula* are malyngamides which are amides of the fatty acid and 7(*S*)-methoxytetradecenoate [33]. Mundt, et al., [7] reported the presence of fatty acid from cyanobacterium *Oscillatoria redeki* HUB051 which showed antibacterial properties against *B. subtilis SBUG 14, Micrococcus flavus SBUG 16, S. aureus SBUG 11 and S. aureus ATCC 2592. Phormidiun tenue* shows anti HIV activity by the production of fatty acids [34]. Sulfoglycolipid which inhibit reverse transcriptase activity of HIV is produced from *Scytonema* sp. [35]. Antibiotic activity has also been shown by production of linolenic acid from *Synechococcus* sp. [36].

Polyketides

Cryptophycin, first discovered as a fungicide from a *Nostoc* strain in 1990, is the most well-known member of a cyanobacterial product with powerful anticancer effects. It

is made up of a polyketide fragment, a modified D-α-amino acid, a β-amino acid, and a hydroxyl acid, making a depsipeptide, which is typical of cyanobacterial metabolites. It has powerful cytotoxicity against tumor cell lines [37]. The major protease M^{pro} andthe papain-like protease PL^{pro}, two SARS-CoV2 proteases, were used in the study to evaluate the molecular docking of the drugs at their binding pockets. These proteases are crucial targets for the creation of antiviral medications. The depsipeptide cryptophycin 52, one of the cyanometabolites, displayed encouraging results on the two SARS-CoV2 proteases [38]. Moore and coworkers discovered boron-containing polyketide borophycin from *Nostoc linckia* and later *Nostoc spongiaeforme* in 1994, against conventional cancer cell lines, this compound showed promising anticancer activity [39, 40]. The crude extract of *Trichodesmium thiebautii* was used to create the linear polyketide trichopycin A (56), which contains vinyl chloride. Both neuro-2 A cells and HCT-116 cells were moderately cytotoxic to trichopycin A [41]. In 2014, *Trichodesmium erythraeum* from Singapore was used to create two novel polyketides that are analogues of aplysiatoxin: 3-methoxyaplysiatoxin and 3-methoxydebromoaplysiatoxin. Infected SJCRH30 cells were post-treated with 3-methoxydebromoaplysiatoxin, which demonstrated substantial efficacy against the Chikungunya virus [25].

Peptides and proteins

In 1942, peptides that inhibit bacteria were discovered for the first time [42]. They're usually positively charged and have disulfide bonds in them. The development of ion channels in the microbial membrane or competitive suppression of microbial protein adhesion to host polysaccharide receptors could be their mechanism of action [43]. Cyanobacteria have previously yielded many structural groups of peptides, including linear peptides, linear

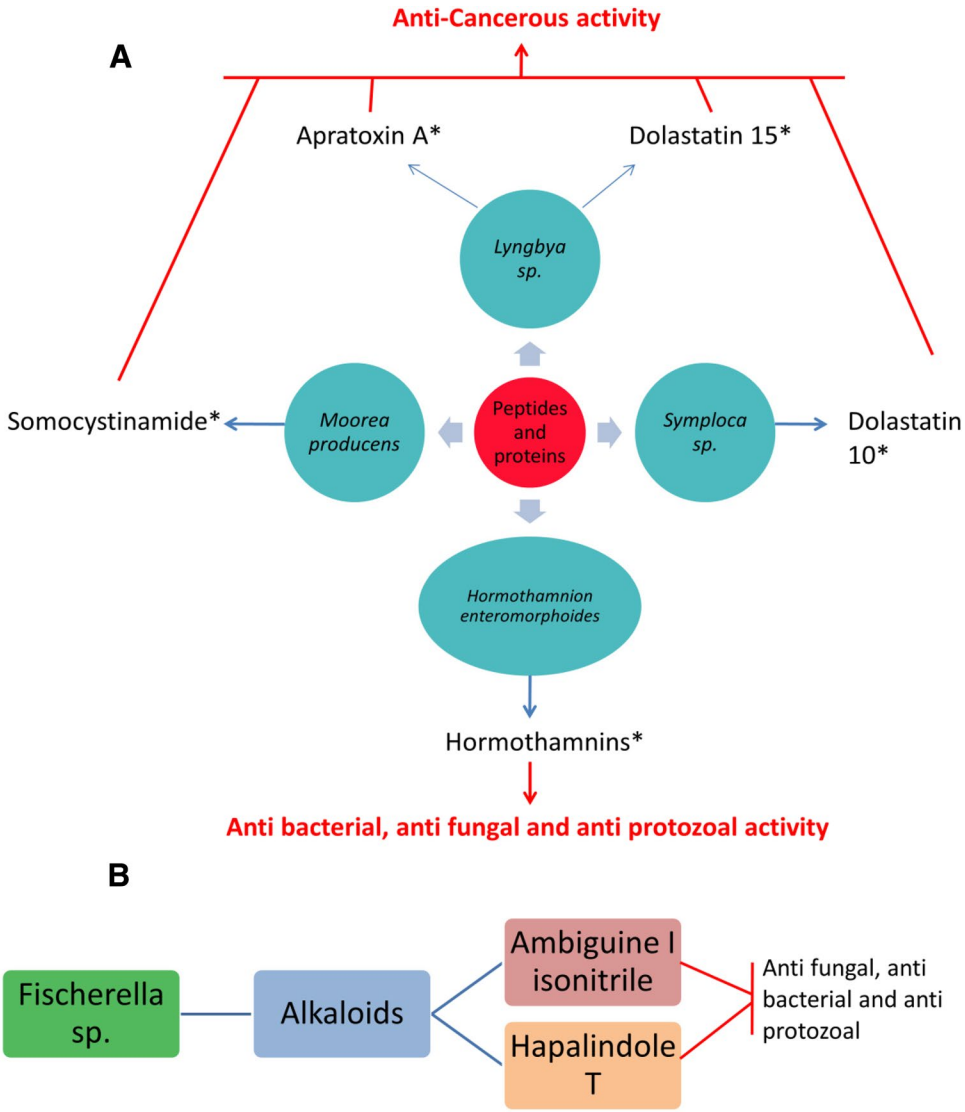


Fig. 2 Anti-microbial activity of cyanobacteria. **A** Anti-cancerous and anti-microbial activity of cyanobacterial metabolites possessing same functional group. *Metabolites. **B** Wide antimicrobial activity of cyanobacterium producing different metabolites with same chemical functional group

Table 1 Classification, structure of various cyanobacterial metabolites possessing antimicrobial activity

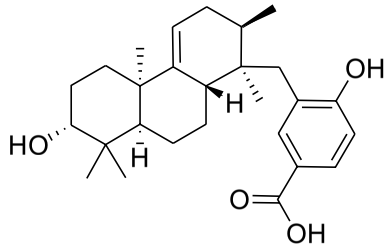
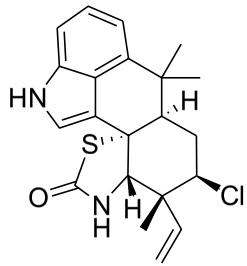
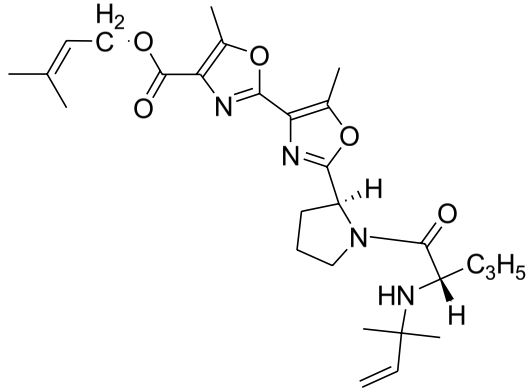
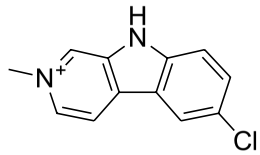
Metabolites	Compounds	Structures	Source	Active against	References
Terpenes and terpenoids	Noscomin		*Nostoc commune*	*Bacillus cereus, Staphylococcus epidermidis*, and *Escherichia coli*	[8]
Alkaloids	Hapalindole T		*Fischerella* sp.	*S. aureus, Pseudomonas aeruginosa, Salmonella Typhi, E. coli*	[65]
	Muscoride A		*Nostoc muscorum*	Antibacterial against wide range of bacteria	[16]
	Nostocarboline		*Nostoc* sp.	*Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani* and *Plasmodium falciparum*	[66]

Table 1 (continued)

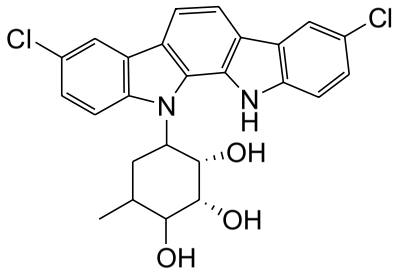
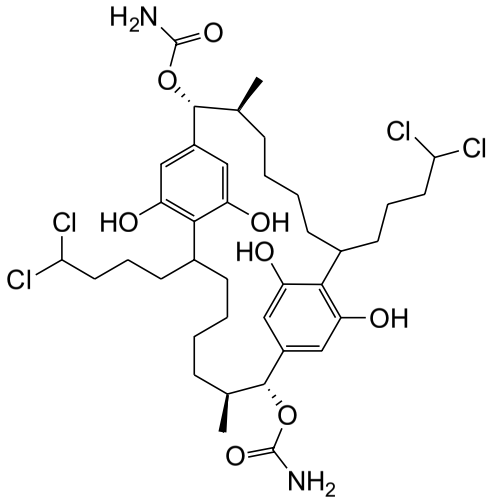
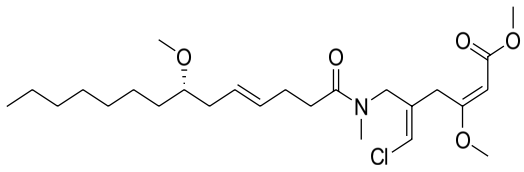
Metabolites	Compounds	Structures	Source	Active against	References
	Tjipanazoles		*Tolypothrix tjipanasensis*	Antifungal	[19]
	Carbamidocyclophane A		*Nostoc* sp. CAVN 10	*Staphylococcus aureus*	[67]
Carbohydrate	Nostoflan	-4)-D-Glcp-(1-, -6,4)-D-Glcp- (1-, −4)-D-Galp-(1-, -4)-D-Xylp-(1-, D-GlcAp-(1-, D-Manp-(1- with a ratio of 1:1:1:1:0.8:0.2	*Nostoc flagelliforme*	HSV-1, HSV-2, human cytomegalovirus	[27]
	Calcium spirulan (Ca-SP)	Sulphated polysaccharide composed of O-rhamnosyl-acofriose and O-hexuronosylrhamnose	*Spirulina platensis*	HIV-1, HSV-1, measles virus, mumps virus, influenza A virus and human cytomegalo virus	[28]
Fatty acid	Malyngamides O		*Moorea producens*	Antibacterial against wide range of bacteria	[33]

Table 1 (continued)

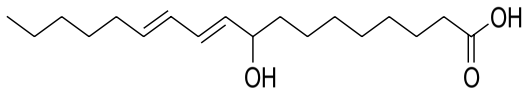
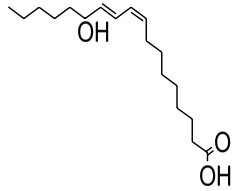
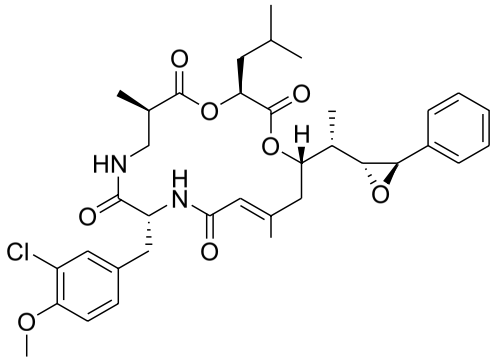
Metabolites	Compounds	Structures	Source	Active against	References
	Fatty acid	 	*Oscillatoriaredeki* HUB051	*B. subtilis SBUG 14*, *Micrococcus flavus SBUG 16, S. aureus SBUG 11, S. aureus ATCC 25,923*	[7]
	Sulfoglycolipids	Sulfoquinovosyldiacylglyerols	*Scytonema* sp.	Inhibit reverse transcriptase activity of HIV	[35]
Polyketides	Cryptophycin		*Nostoc* sp. GSV224	Suppressor of microtubule dynamics and blocks the cells in G2/M phase	[37]

Table 1 (continued)

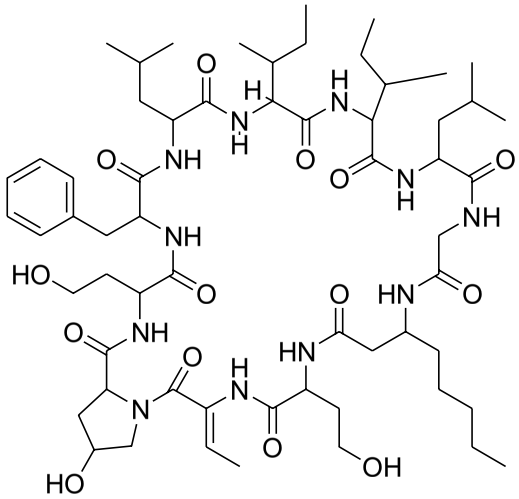
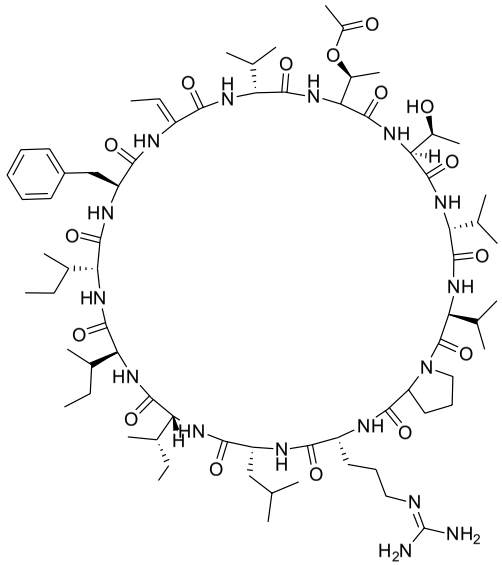
Metabolites	Compounds	Structures	Source	Active against	References
Peptides and proteins	Hormothamnin		*Hormothamnion enteromorphoides*	*Staphylococcus aureus, Bacillus subtilis, Streptococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Salmonella typhimurium*	[68]
	Tolybyssidins		*Tolypothrix byssoidea*	Antifungal	[52]

Table 1 (continued)

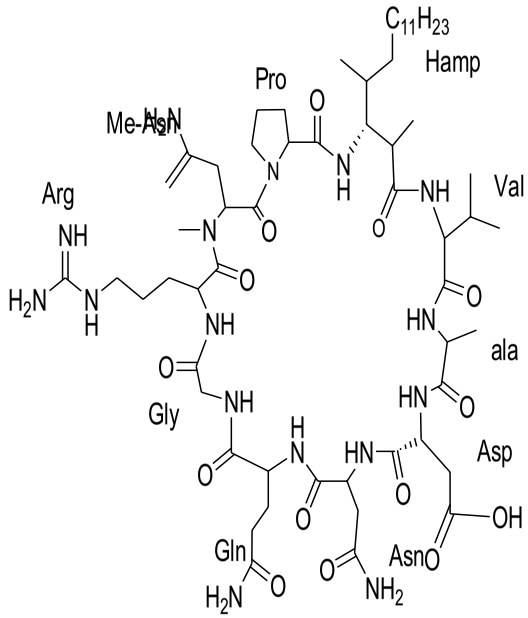
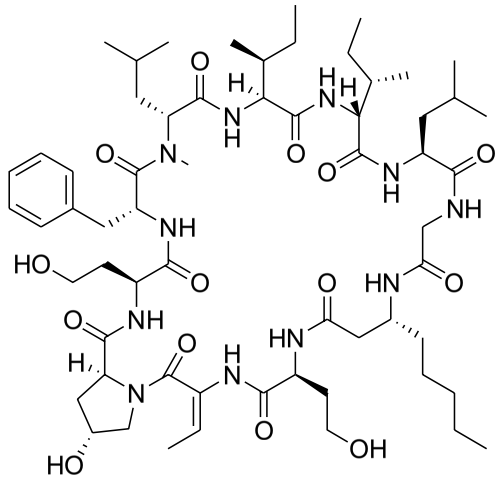
Metabolites	Compounds	Structures	Source	Active against	References
	Calophycin		*Calothrix fusca*	Antifungal	[56]
	Laxaphycin		*Anabaena laxa*	Antifungal	[69]

Table 1 (continued)

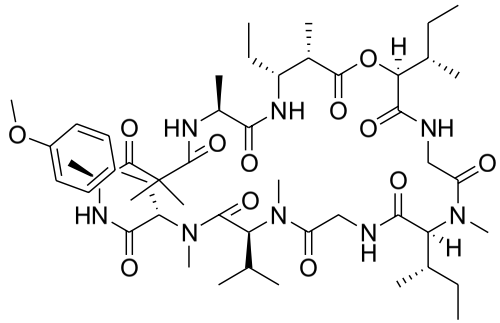
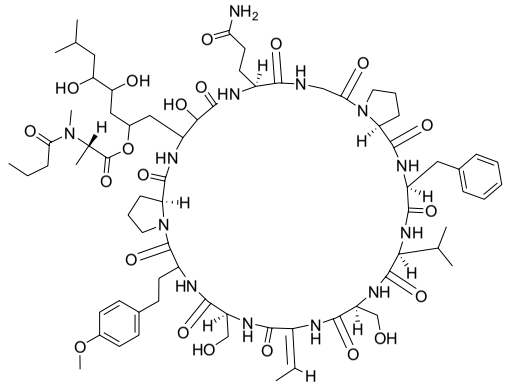
Metabolites	Compounds	Structures	Source	Active against	References
	Majusculamide C		*Moorea producens*	Antifungal	[70]
	Schizotrin A		*Schizothrix* sp.	Antifungal	[71]
	Cyanovirin-N	(NH2) Leu–Gly–Lys–Phe–Scr–Ghs–Thr–Cys–Tyr–Asn–Ser–Ala– Ile–Gln–Gly–Ser–Val–Len–Thr–Ser–The–Cys–Glu–Arg–Thr–Asn– Gly–Gly–Thr–Ser–The–Ser–Ser–Ilg–Asp–Leu–Asn–Ser–Val–Ile– Glu–Asn–Val–Asp–Gly–Ser–Len–Lys–Trp–Gln–Pro–Ser–Asn–Phe– Ile–Glu–Thr–Cys–Arg–Asn–Thr–Gln–Leu–Ata–Gly–Ser–Ser–Glu– Leu–Ala–Ala–Glu–Cys–Lys–Thr–Arg–Ala–Glu–Gln–Phe–Val–Ser– Thr–Lys–Ile–Asn–Leu–Asp–Asp–His–Ile–Ala–Asn–Ile–Asp–Gly– Tla–Leu–Lys–Thr–Gla (COOH)	*Nostocellipsosporum*	Anti HIV bind to gp 120	[72]

Table 1 (continued)

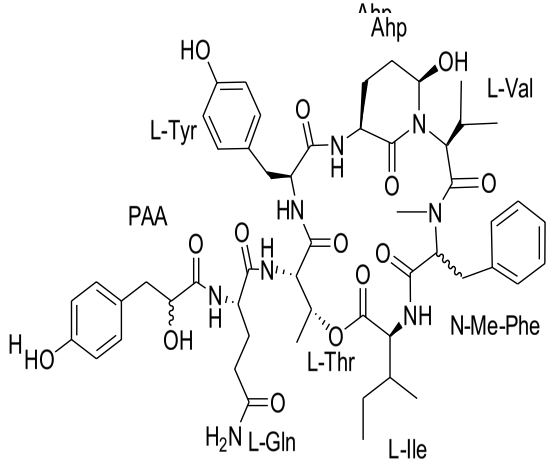
Metabolites	Compounds	Structures	Source	Active against	References
	Scytovirin-N	Domain-1 (NH2) Ala–Ala–Ala–His–Gly–Ala–Thr–Gly–Gln–Cys– Phe–Gly–Ser–Ser–Ser–Cys–Thr–Arg–Ala–Gly–asp–Cyst–Gln–Lys– Ser–Asn–Ser–Cys–Arg–Asn–Pro–Gly–Gly–Pro–Asn–Lys–Ala–Glu– asp–Trp–Cys–Tyr–Thr–Pro–Gly–Lys–Pro– Domain-2 Gly–Pro–Asp–Pro–Lys–Arg–Ser–Thr–Gly–Gln–Cys– Phe–Gly–Ser–Ser–Ser–Cys–Thr–Arg–Ala– Gly–asp–Cys–Gln–Lys– Asn–Asn–Ser–Cys–Arg–Asn–Pro–Gly–Gly–Pro–Asn–Asn–Ala–Glu–Asn–Trp–Cys–Tyr–Thr–Pro–Gly–Ser–Gly (COOH)	*Scytonema varium*	Anti-HIV bind to viral coat proteins gp120, gp160 and gp41	[72]
	Ichthyopeptins A and B	 Ichthyopeptins A	*Microcystis ichthyoblabe*	Influenza A virus	[53]

Table 1 (continued)

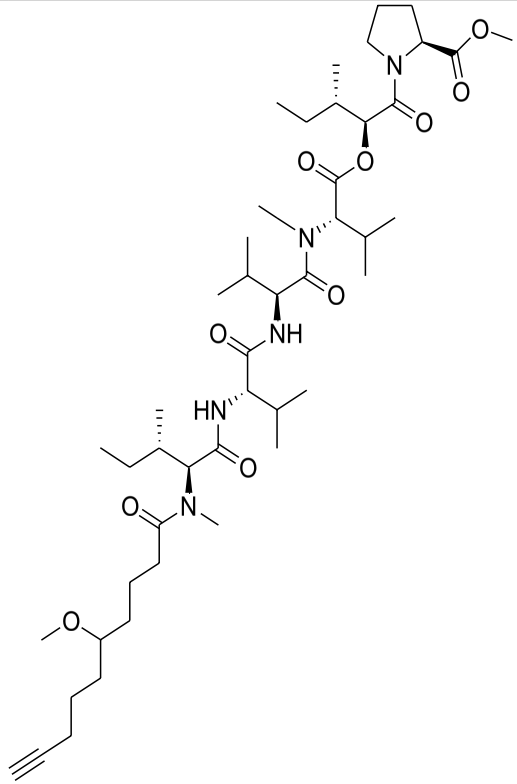
Metabolites	Compounds	Structures	Source	Active against	References
	Viridamide A		*Oscillatorianigro virdis*	*Trypanosoma cruzi, Leishmania mexicana, Plasmodium falciparum*	[63]

Table 1 (continued)

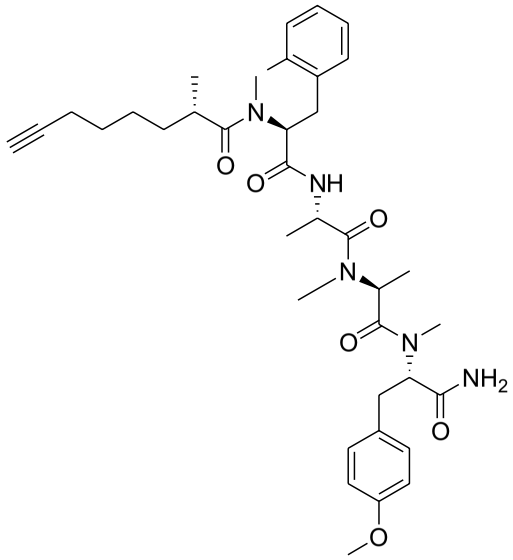
Metabolites	Compounds	Structures	Source	Active against	References
	Dragomabin		*Moorea producens*	*P. falciparum*	[48]

Table 1 (continued)

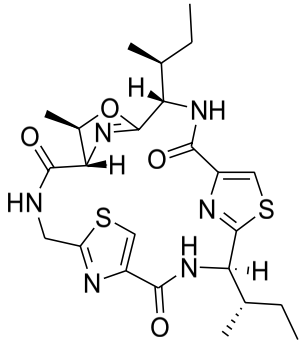
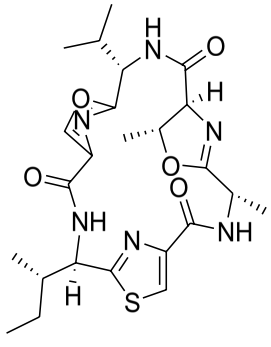
Metabolites	Compounds	Structures	Source	Active against	References
	Aerucyclamide C and B	 AerucyclamideB$_{Aerucy}$  Aerucyclamide C clamide BAerucyclamide C	*Microcystisaerugi-nosa PCC 7806*	*T. brucei* and *P. falciparum*	[64]

Table 1 (continued)

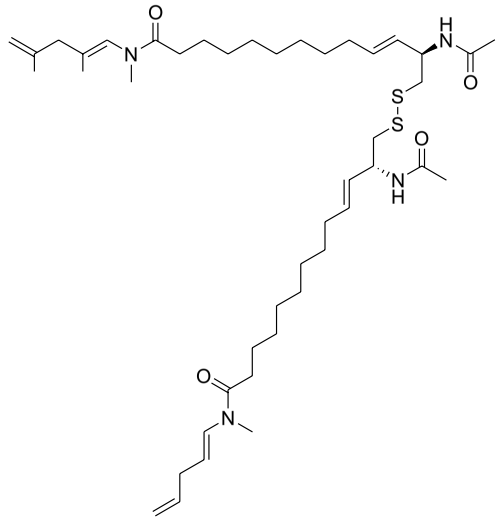
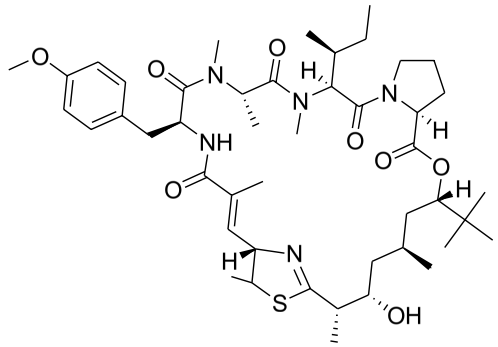
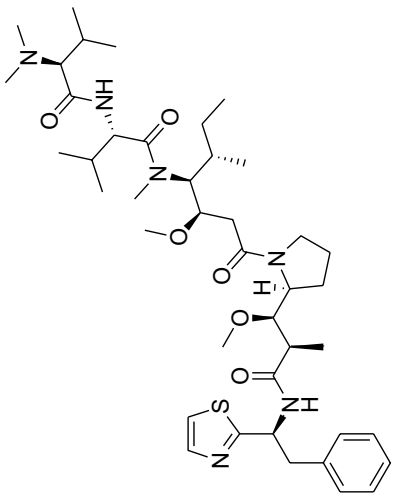
Metabolites	Compounds	Structures	Source	Active against	References
	Somocystinamide A		*Moorea producens*	Induces apoptosis in tumour and angiogenesis endothelial cells	[73]
	Apratoxin A		*Moorea* sp.	Arrest of G-1 phase of cell cycle and apoptosis	[74]

Table 1 (continued)

Metabolites	Compounds	Structures	Source	Active against	References
	Dolastatin 10		*Symploca* sp.	Potent antiproliferative agent and acts by binding to tubulin	[47]

depsipeptides, linear lipopeptides, and cyclic peptides, cyclic depsipeptides, and cyclic lipopeptides [44]. Notably, certain cyanobacterial peptides and associated hybrid metabolites have even advanced as lead molecules for therapeutic use. For instance, the U.S. Food and Drug Administration (FDA) approved brentuximab vedotin (trade name Adcetris), a medication derived from marine peptides, in 2011 for the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma [45].Malyngamides are a type of linear lipopeptide that has become a hallmark of marine cyanobacterial secondary metabolism [46]. Since 2001, five further compounds [malyngamides S to W] have been found, bringing the total number of such molecules isolated from *Lyngbya* sp. to 34. Malyngamides T and U–W were obtained from a Puerto Rican and a Papua New Guinea collection of *L. majuscula*, respectively [47]. Dragomabin, a linear peptide isolated from *Moorea producens* with antiprotozoal activity against *P. falciparum* [48]. Dolastatin 10, a cyanobacterial metabolite, isolated from *Symploca* sp. [49], is a pentapeptide containing four unique amino acids, dolavaline, dolaisoleucine, dolaproline and dolaphenine and is a potent antiproliferative agent and acts by binding to tubulin on the rhizoxin-binding site, affecting microtubule assembly. Thus, arresting the cell into G2/M phase. Wrasidlo et al.,2008 [50], isolated Somocystinamide A (ScA) from *Moorea producens*, is a lipopeptide which is pluripotent inhibitor of angiogenesis and tumor cell proliferation and functions by inducing apoptosis in tumour and angiogenic endothelial cells. Antimicrobial activity has been found for a variety of cyclic peptides and depsipeptides isolated from cyanobacteria. These include tenuecyclamides which are antibacterial and cytotoxic agents isolated from the lithophytic cyanobacterium *Nostoc spongiaeforme var. tenue* [40], schizotrin A, an antifungal and antibacterial compound from *Schizothrix* sp. [51], hormothamnins (antibacterial and antifungal compounds) from the marine cyanobacterium *Hormothamnion* [52]. Ickthyopeptins A and B, cyclic depsipeptides isolated from the cyanobacterium *Microcystis ichthyoblabe*, have antiviral action against the influenza A virus [53]. Apratoxin A, a cyclodepsipeptide isolated from *a Moorea sp*. is cytotoxic to human tumor cell lines [54] by inducing the arrest of G-1 phase cell cycle and apoptosis [55]. *Calothrix fusca* [56] and *Tolypothrix byssoidea* [52] produces calophycin and tolybyssidins, respectively, which are antifungal in nature. Laxaphycins from *Anabaena laxa* [57, 58], majusculamide C from *Moorea producens* [59] possess both antifungal and antibacterial properties. Carbohydrate binding protein, Cyanovirin-N, isolated from *Nostoc ellipsosporum*, exhibits antiviral activity, it has been found to be a potent anti-HIV and it inhibit the HIV activity by binding to its gp 120, a surface envelope glycoprotein and further inhibiting the fusion of

virus with the cellular receptor CD4 [60]. Cyanovirin-N was identified with the S glycoprotein of SARS-CoV-2 and was found to have the highest concentration among other lectins using molecular docking and MD simulation experiments. Lokhande demonstrated that binding complexes between BanLec in its wild-type and mutant forms are more thermodynamically stable [61]. Scytovirin, another carbohydrate binding protein isolated by Bokesch et al., 2003 [62] from aqueous extract of *Scytonema varium*is a potent anti-HIV protein that acts by binding to viral coat proteins gp120, gp160 and gp41. The Panamanian International Co-operative Biodiversity Group has reported the isolation of antiprotozoal compounds from cyanobacteria. Viridamide A isolated from *Oscillatoria nigro Virdis*, is active against *Trypanosoma cruzi, Leishmania mexicana, Plasmodium falciparum*[63]. Aerucyclamide C and aerucyclamide B (heterocyclic ribosomal peptide) isolated from *Microcystis aeruginosa* PCC 7806 is active against *T. brucei* and *P. falciparum*, respectively [64].

Discussion

Cyanobacteria are cosmopolitan, oxygenic photosynthetic bacteria and are found in diverse habitat. They have been recognised recently for their potential to produce therapeutic compounds. Present review article compiled therapeutic potential of cyanobacterial metabolites in terms of chemical functional group (Table 1). Moreover, it has also been reported that many of them are capable of producing more than one kind of metabolite with same functional group which either act against wide spectrum of microbes or act on single microbe (Fig. 2). Though much research has been done to extract various metabolic compounds possessing antimicrobial activity using numerous procedures and protocols but further research is needed in this field for proper understanding of action mechanism as very few cyanobacterial metabolites have entered clinical trials and till date only brentuximab vedotin (trade name Adcetris), a medication derived from marine peptides, for the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma has been approved by FDA (Food and Drug Administration). Therefore, the field of phycochemistry requires more intensive and interdisclipinary research and many clinical trials need to be take place in order to establish them as a source of antimicrobial agent or anti cancerous agent. Moreover, there is need to explore cyanobacteria as therapeutic agent in order to produce alternative source of drugs because it is cost effective as cyanobacteria is easy to maintain in culture condition due to its ability to harbour in simple inorganic nutrient condition and many of them show wide spectrum activity against microbes.

Conclusion

The review article compiled therapeutic potential of cyanobacterial metabolites in terms of phycochemistry. Cyanobacterial metabolites display fascinating and broad bioactivity and numerous techniques are employed for extraction, isolation and purification of these cyanobacterial bioactive metabolites. However, most of the research has been focused on model organisms such as *Synechocystis* sp. PCC 6803 and *Anabaena* PCC7120 particularly towards abiotic stress-induced modifications of gene and protein expression such as response to salinity, UV-B, heat, high light intensities and nutrient deprivation etc. Another field that is much studied is engineering of cyanobacteria for biofuel production. Nevertheless, taking recourse to pharmaceutical importance of cyanobacterial metabolites, more attention is needed to explore cyanobacteria as a source of therapeutic compound to find more novel antimicrobial compound and to fully understand the mechanisms of action linked to cyanobacterial metabolites, additional in vivo research is still required. For instance, nostoflan showed strong antiviral efficacy against type 1 of the herpes simplex virus (HSV-1). The broad-spectrum antiviral calcium spirulan supplement has an effect on the reduction of human viruses' ability to replicate in vitro, including HCMV, HSV-1, HHV-6, and HIV-1. Together, these signs suggest that cyanobacterial products may play a role in the fight against coronaviruses, which calls for more research into testing cyanobacterial secondary metabolites against SARS-CoV-2 and in particular to combat the COVID-19 pandemic. Furthermore, cyanobacteria from unexplored and extremes of environment should also be studied in order to discover novel compounds.

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Declarations

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References

1. Bassett EJ et al (1980) Tetracycline-labeled human bone from ancient Sudanese Nubia (AD 350). Science 209(4464):1532–1534
2. Nelson ML et al (2010) Brief communication: mass spectroscopic characterization of tetracycline in the skeletal remains of an ancient population from Sudanese Nubia 350–550 CE. Am J Phys Anthropol 143(1):151–154
3. Cook M, Molto E, Anderson C (1989) Fluorochrome labelling in Roman period skeletons from Dakhleh Oasis. Egypt Am J Phys Anthropol 80(2):137–143
4. Schwarzer D, Finking R, Marahiel MA (2003) Nonribosomal peptides: from genes to products. Nat Prod Rep 20(3):275–287
5. Foster RA et al (2011) Nitrogen fixation and transfer in open ocean diatom–cyanobacterial symbioses. ISME J 5(9):1484–1493
6. Anjum K et al (2017) Emerging biopharmaceuticals from bioactive peptides derived from marine organisms. Chem Biol Drug Des 90(1):12–30
7. Mundt S, Kreitlow S, Jansen R (2003) Fatty acids with antibacterial activity from the cyanobacterium *Oscillatoria redekei* HUB 051. J Appl Phycol 15(2–3):263–267
8. Jaki B, Orjala J, Sticher O (1999) A novel extracellular diterpenoid with antibacterial activity from the cyanobacterium *Nostoc commune*. J Nat Prod 62(3):502–503
9. Mo S et al (2009) An antimicrobial guanidine-bearing sesterterpene from the cultured cyanobacterium *Scytonema* sp. J Nat Prod 72(11):2043–2045
10. Cabanillas AH et al (2018) *Cybastacines* A and B: antibiotic sesterterpenes from a *Nostoc* sp. cyanobacterium. J Nat Prod 81(2):410–413
11. Shah SAA et al (2017) Structural diversity, biological properties and applications of natural products from cyanobacteria. Rev Mar drugs 15(11):354
12. Fessenden R, Fessenden J (1982) Organic chemistry. Willard Grant Press, Boston, Mass
13. Moore RE et al (1987) Hapalindoles, antibacterial and antimycotic alkaloids from the cyanophyte *Hapalosiphon fontinalis*. J Org Chem 52(6):1036–1043
14. Smitka TA et al (1992) Ambiguine isonitriles, fungicidal hapalindole-type alkaloids from three genera of blue-green algae belonging to the Stigonemataceae. J Org Chem 57(3):857–861
15. Park A, Moore RE, Patterson GM (1992) Fischerindole L, a new isonitrile from the terrestrial blue-green alga *Fischerella muscicola*. Tetrahedron Lett 33(23):3257–3260
16. Nagatsu A, Kajitani H, Sakakibara J (1995) Muscoride A: a new oxazole peptide alkaloid from freshwater cyanobacterium *Nostoc muscorum*. Tetrahedron Lett 36(23):4097–4100
17. Barbaras D et al (2008) Potent and selective antiplasmodial activity of the cyanobacterial alkaloid nostocarboline and its dimers. Bioorg Med Chem Lett 18(15):4413–4415
18. Blom JF et al (2006) Potent algicides based on the cyanobacterial alkaloid nostocarboline. Org Lett 8(4):737–740
19. Bonjouklian R et al (1991) Tjipanazoles, new antifungal agents from the blue-green alga *Tolypothrix tjipanasensis*. Tetrahedron 47(37):7739–7750
20. Stewart JB et al (1988) Cytotoxic, fungicidal nucleosides from blue green algae belonging to the Scytonemataceae. J Antibiot 41(8):1048–1056
21. Moore BS et al (1990) [7.7] Paracyclophanes from blue-green algae. J Am Chem Soc 112(10):4061–4063
22. Saker ML, Eaglesham GK (1999) The accumulation of cylindrospermopsin from the cyanobacterium *Cylindrospermopsis raciborskii* in tissues of the Redclaw crayfish Cherax quadricarinatus. Toxicon 37(7):1065–1077
23. Naidoo D et al (2021) Cyanobacterial metabolites as promising drug leads against the Mpro and PLpro of SARS-CoV-2: an in silico analysis. J Biomol Struct Dyn 39(16):6218–6230
24. Bhateja P et al (2006) Activity of blue green microalgae extracts against in vitro generated *Staphylococcus aureus* with reduced susceptibility to vancomycin. Fitoterapia 77(3):233–235
25. Zhang C et al (2017) Laucysteinamide a, a hybrid PKS/NRPS metabolite from a Saipan Cyanobacterium, cf. *Caldora penicillata*. Mar Drugs 15(4):121
26. Soares AlR et al (2015) Carriebowlinol, an antimicrobial tetrahydroquinolinol from an assemblage of marine cyanobacteria containing a novel taxon. J Nat Prod 78(3):534–538
27. Kanekiyo K et al (2005) Isolation of an antiviral polysaccharide, nostoflan, from a terrestrial cyanobacterium, *Nostoc flagelliforme*. J Nat Prod 68(7):1037–1041
28. Feldman SC et al (1999) Antiviral properties of fucoidan fractions from *Leathesia difformis*. Phytomedicine 6(5):335–340
29. Hayashi K, Hayashi T, Kojima I (1996) A natural sulfated polysaccharide, calcium spirulan, isolated from *Spirulina platensis*: in vitro and ex vivo evaluation of anti-herpes simplex virus and anti-human immunodeficiency virus activities. AIDS Res Hum Retrovi 12(15):1463–1471
30. Khalifa SA et al (2021) Cyanobacteria—from the oceans to the potential biotechnological and biomedical applications. Mar Drugs 19(5):241
31. Murakami N et al (1991) Studies on glycolipids. III. Glyceroglycolipids from an axenically cultured cyanobacterium, *Phormidium tenue*. Chem Pharm Bull 39(9):2277–2281
32. Sijtsma L, De M (2004) Biotechnological production and applications of the ω-3 polyunsaturated fatty acid docosahexaenoic acid. Appl Microbiol Biotechnol 64(2):146–153
33. Gekwick WH, Reyes S, Alvarado B (1987) Two malyngamides from the Caribbean cyanobacterium *Lyngbya majuscula*. Phytochemistry 26(6):1701–1704
34. Gustafson KR et al (1989) AIDS-antiviral sulfolipids from cyanobacteria (blue-green algae). JNCI 81(16):1254–1258
35. Loya S et al (1998) The inhibition of the reverse transcriptase of HIV-1 by the natural sulfoglycolipids from cyanobacteria: contribution of different moieties to their high potency. J Nat Prod 61(7):891–895
36. Ohta S et al (1994) Anti methicillin-resistant *Staphylococcus aureus* (MRSA) activity by linolenic acid isolated from the marine microalga *Chlorococcum* HS-101. Bull Environ Contam Toxicol 52(5):673–680
37. Kumar A et al (2017) Antibody-drug conjugates, annual reports in medicinal chemistry. Elsevier, Amsterdam, pp 441–480
38. Mazur-Marzec H et al (2021) Antiviral cyanometabolites—a review. Biomolecules 11(3):474
39. Hemscheidt T et al (1994) Structure and biosynthesis of borophycin, a new boeseken complex of boric acid from a marine strain of the blue-green alga *Nostoc linckia*. J Org Chem 59(12):3467–3471
40. Banker R, Carmeli S (1998) Tenuecyclamides A–D, Cyclic hexapeptides from the cyanobacterium *Nostoc spongiaeforme var. tenue*. J Nat Prod 61(10):1248–1251
41. Bertin MJ et al (2017) Trichophycin A, a cytotoxic linear polyketide isolated from a *Trichodesmium thiebautii* bloom. Mar Drugs 15(1):10
42. Balls A, Hale W, Harris T (1942) A crystalline protein obtained from a lipoprotein of wheat flour. Cereal Chem 19(19):279–288
43. Zhang Y, Lewis K (1997) Fabatins: new antimicrobial plant peptides. FEMS Microbiol Lett 149(1):59–64

44. Singh R et al (2017) Uncovering potential applications of cyanobacteria and algal metabolites in biology, agriculture and medicine: current status and future prospects. Front Microbiol 8:515
45. Minich SS (2012) Brentuximab vedotin: a new age in the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma. Ann Pharmacother 46(3):377–383
46. Gerwick WH, Tan LT, Sitachitta N (2001) Nitrogen-containing metabolites from marine cyanobacteria. Academic Press, San Diego
47. Tan LT (2007) Bioactive natural products from marine cyanobacteria for drug discovery. Phytochemistry 68(7):954–979
48. McPhail KL et al (2007) Antimalarial linear lipopeptides from a panamanian strain of the marine cyanobacterium *Lyngbya majuscula*. J Nat Prod 70(6):984–988
49. Luesch H et al (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(7):907–910
50. Wrasidlo W et al (2008) The marine lipopeptide somocystinamide A triggers apoptosis via caspase 8. Proc Natl Acad Sci USA 105(7):2313–2318
51. Pergament I, Carmeli S (1994) Schizotrin A; a novel antimicrobial cyclic peptide from a cyanobacterium. Tetrahedron Lett 35(45):8473–8476
52. Jaki B et al (2001) Two novel cyclic peptides with antifungal activity from the Cyanobacterium *Tolypothrix byssoidea* (EAWAG 195). J Nat Prod 64(2):154–158
53. Zainuddin EN et al (2007) Cyclic depsipeptides, ichthyopeptins A and B, from *Microcystis ichthyoblabe*. J Nat Prod 70(7):1084–1088
54. Luesch H et al (2001) Total structure determination of Apratoxin A, a potent novel cytotoxin from the marine cyanobacterium *Lyngbya majuscula*. J Am Chem Soc 123(23):5418–5423
55. Luesch H et al (2006) A functional genomics approach to the mode of action of apratoxin A. Nat Chem Biol 2(3):158
56. Moon SS et al (1992) Calophycin, a fungicidal cyclic decapeptide from the terrestrial blue-green alga *Calothrix fusca*. J Org Chem 57(4):1097–1103
57. Frankmolle WP et al (1992) Antifungal cyclic peptides from the terrestrial blue-green alga *Anabaena laxa*. J Antibiot 45(9):1451–1457
58. Frankmolle WP et al (1992) *Antifungal* cyclic peptides from the terrestrial blue-green alga *Anabaena laxa. II*. Structures of laxaphycins A, B, D and E. J Antibiot 45(9):1458–1466
59. Carter DC et al (1984) Structure of majusculamide C, a cyclic depsipeptide from *Lyngbya majuscula*. J Org Chem 49(2):236–241
60. Boyd MR et al (1997) Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: potential applications to microbicide development. Antimicrob Agents Chemother 41(7):1521–1530
61. Lokhande KB et al (2022) Sensing the interactions between carbohydrate-binding agents and N-linked glycans of SARS-CoV-2 spike glycoprotein using molecular docking and simulation studies. J Biomol Struct Dyn 40(9):3880–3898
62. Bokesch HR et al (2003) A potent novel anti-HIV protein from the cultured cyanobacterium *Scytonema varium*. Biochemistry 42(9):2578–2584
63. Simmons TL et al (2008) Viridamides A and B, lipodepsipeptides with antiprotozoal activity from the marine cyanobacterium *Oscillatoria nigro-viridis*. J Nat Prod 71(9):1544–1550
64. Portmann C et al (2008) Isolation of aerucyclamides C and D and structure revision of microcyclamide 7806A: heterocyclic ribosomal peptides from *Microcystis aeruginosa PCC 7806* and their antiparasite evaluation. J nat prod 71(11):1891–1896
65. Asthana RK et al (2006) Identification of an antimicrobial entity from the cyanobacterium *Fischerella* sp. isolated from bark of *Azadirachta indica* (Neem) tree. J Appl Phycol 18(1):33–39
66. Becher PG et al (2005) Nostocarboline: isolation and synthesis of a new cholinesterase inhibitor from *Nostoc 78-12A*. J Nat Prod 68(12):1793–1795
67. Bui HT et al (2007) Carbamidocyclophanes A–E, chlorinated paracyclophanes with cytotoxic and antibiotic activity from the vietnamese cyanobacterium *Nostoc* sp. J Nat Prod 70(4):499–503
68. Gerwick WH et al (1992) Total structure of hormothamnin A, a toxic cyclic undecapeptide from the tropical marine cyanobacterium *Hormothamnion enteromorphoides*. Tetrahedron 48(12):2313–2324
69. Bornancin L et al (2019) Structure and biological evaluation of new cyclic and acyclic laxaphycin-A type peptides. Bioorg Med Chem 27(10):1966–1980
70. Mesguiche V et al (1999) Characterization and synthesis of (–)-7-methoxydodec-4(E)-enoic acid, a novel fatty acid isolated from *Lyngbya majuscula*. Tetrahedron Lett 40(42):7473–7476
71. Liu L, Rein KS (2010) New peptides isolated from *Lyngbya species*: a review. Mar Drugs 8(6):1817–1837
72. Singh RK et al (2011) Cyanobacteria: an emerging source for drug discovery. J Antibiot 64(6):401
73. Nogle LM, Gerwick WH (2002) Somocystinamide A, a novel cytotoxic disulfide dimer from a Fijian marine cyanobacterial mixed assemblage. Org Lett 4(7):1095–1098
74. Huang KC et al (2016) Apratoxin A shows novel pancreas-targeting activity through the binding of sect. 61. Mol Cancer Ther 15(6):1208–1216