Phycochemistry and bioactivity of cyanobacterial secondary metabolites

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Abstract
Microbes are huge contributors 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 Nabi, 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...
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, phototrophically 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 polypeptide-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 mediation 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,
God of sleep [12]. Hapalindoles, an indolealkoid produced by *Hapalosiphon fontinalis* [13] exhibit antibacterial anti-fungal properties. Hapalinolide-type alkaloids, ambiguine isonitriles, exhibiting fungicidal activity, are produced by cyanobacterial species *Fischereilla ambiguca, Hapalosiphon hibernicus* and *Westiellopsis prolific* [14]. *Fischereilla muscicola*, a terrestrial cyanobacterium, has been shown to produce fischerindole L, an antifungal molecule that is chemically linked to hapalinolides [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, nostocaroline, isolated from *Nostoc sp.* found to be active against *Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani* and *Plasmodium falciparum* [17]. Nostocaroline 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 didehydrodromirirazole which possess antibiotic and cytotoxic activity [20]. *Cylindrospermum licheniforme* and *Cylindrospermopsis raciborskii* produces alkaloids cylindrocyclophane and cylindropermpin which are anticancerous and cytotoxic in nature, repectively [21, 22]. Moreover, cylindropermpin exhibited promising inhibitory potential against the SARS-CoV-2 M<sup>PRO</sup> (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]. *Callorella 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 anti-microbial compound. *Nostoc flagelliforme* is known to produce nostoflan, an antiviral acidic polysaccharide, having virucidal activity against HIV-1, HSV-2, human cytomegalovirus and influenza A virus [27]. Apart from nostoflan, Calcium spirulan (Ca-SP), a natural sulphated polysaccharide, from *Spirulina platensis*, 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 anti-biotic effects in the pulmonary tissues. It was shown that the polysaccharides generated from various *Spirulina* species, particularly *Spirulina platensis*, has 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 eicosapentenoic 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*. *Phormidium 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 Mpro and the papain-like protease PLpro, 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...
| Metabolites                  | Compounds        | Structures                                   | Source        | Active against                                                                 | References |
|-----------------------------|------------------|----------------------------------------------|---------------|--------------------------------------------------------------------------------|------------|
| Terpenes and terpenoids     | Noscomin         | ![Noscomin Structure](image)                 | *Nostoc commune* | *Bacillus cereus, Staphylococcus epidermidis, and Escherichia coli*             | [8]        |
| Alkaloids                   | Hapalindole T    | ![Hapalindole T Structure](image)            | *Fischerella sp.* | *S. aureus, Pseudomonas aeruginosa, Salmonella Typhi, E. coli*                  | [65]       |
|                             | Muscoride A      | ![Muscoride A Structure](image)              | *Nostoc muscorum* | Antibacterial against wide range of bacteria                                     | [16]       |
| Nostocarboline              |                  | ![Nostocarboline Structure](image)           | *Nostoc sp.*   | *Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani and Plasmodium falciparum* | [66]       |
| Table 1 (continued) | Metabolites | Compounds | Structures | Source | Active against | References |
|---------------------|-------------|-----------|------------|--------|----------------|------------|
| Tjipanazoles        | Carbamidocyclophane A | Nostoflan | 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) | Calcium spirulan (Ca-SP) | Sulphated polysaccharide composed of O-rhamnosyl-acofriose and O-hexuronosyl-hamnose | 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] |
| Metabolites       | Compounds             | Structures          | Source                  | Active against                                      | References |
|------------------|-----------------------|---------------------|-------------------------|-----------------------------------------------------|------------|
| Fatty acid       |                       |                      | Oscillatoriredeki       | B. subtilis SBUG 14, Micrococcus flavus, SBUG 16, S. aureus SBUG 11, S. aureus ATCC 25,923 | [7]        |
| Sulfoglycolipids | Sulfoglycolipids      | 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]                                                |
| Metabolites               | Compounds          | Structures                                                                 | Source                      | Active against                                                                 | References |
|--------------------------|--------------------|---------------------------------------------------------------------------|-----------------------------|--------------------------------------------------------------------------------|------------|
| Peptides and proteins    | Hormothamnin       | ![Hormothamnin Structure](image)                                           | *Hormothamnion enteromorphoides* | *Staphylococcus aureus, Bacillus subtilis, Streptococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Salmonella typhimurium* | [68]       |
| Tolybyssidins             | Tolythrix bysoideae | ![Tolybyssidins Structure](image)                                         | *Tolythrix bysoideae*       | Antifungal                                                                    | [52]       |
| Metabolites   | Compounds | Structures | Source       | Active against | References |
|--------------|-----------|------------|--------------|----------------|------------|
| Calophycin   |           | ![Calophycin Structure](image) | *Calothrix fusca* | Antifungal     | [56]       |
| Laxaphycin   |           | ![Laxaphycin Structure](image) | *Anabaena laxa* | Antifungal     | [69]       |
| 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–Ser–Val–Len–Thr–Ser–The–Cys–Glu–Arg–Thr–Asn–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]       |
| 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–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–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](image)                                                                       | *Microcystis ichthyoblabe* | Influenza A virus                                   | [53]       |
| Metabolites | Compounds | Structures | Source | Active against | References |
|------------|-----------|------------|--------|----------------|------------|
| Viridamide A | | | Oscillatoria nigro-viridis | Trypanosoma cruzi, Leishmania mexicana, Plasmodium falciparum | [63] |
| Metabolites | Compounds | Structures | Source | Active against | References |
|-------------|-----------|------------|--------|----------------|------------|
| Dragomabin   |           | ![](image) | Moorea producens | P. falciparum | [48]       |
| Metabolites          | Compounds | Structures | Source            | Active against          | References |
|---------------------|-----------|------------|-------------------|-------------------------|------------|
| Aerucyclamide C     | and B     |            | *Microcystis aeruginosa* PCC 7806 | *T. brucei* and *P. falciparum* | [64]       |

![Chemical structures](https://example.com/structures)
| 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] |
depsipeptides, linear lipopeptides, and cyclic peptides, 
cyclic depsipeptides, and cyclic lipopeptides [44]. Nota-
bly, certain cyanobacterial peptides and associated hybrid 
metabolites have even advanced as lead molecules for ther-
apeutic use. For instance, the U.S. Food and Drug Admin-
istration (FDA) approved brentuximab vedotin (trade name 
Adcetris), a medication derived from marine peptides, in 
2011 for the treatment of Hodgkin lymphoma and ana-
plastic 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 mol-
ecules 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 produ-
cens 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, dolaprop-
line 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. Wrasdil et al., 2008 [50], isolated 
Somocystinamide A (ScA) from Moorea producens, is a 
lipopeptide which is pluripotent inhibitor of angiogen-
esis and tumor cell proliferation and functions by induc-
ing apoptosis in tumour and angiogenic endothelial cells. 
Antimicrobial activity has been found for a variety of 
cyclic peptides and depsipeptides isolated from cyanobac-
teria. These include tenuecyclamides which are anti-
bacterial and cytotoxic agents isolated from the lithophytic 
cyanobacterium Nostoc spongiaeformae var. tenue [40], 
schizotrin A, an antifungal and antibacterial compound 
from Schizothrix sp. [51], hormothammins (antibacterial 
and antifungal compounds) from the marine cyanobacte-
rium Hormothamnion [52]. Ickthyopeptins A and B, cyclic 
depsipeptides isolated from the cyanobacterium Microcys-
tis 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 Tolyphothrix bys-
soides [52] produces calophycin and tolybyssidins, respec-
tively, 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
from ucyclamide B (heterocyclic ribosomal peptide) isolated from T. brucei and [63]. Aerucyclamide C and aerucyclamide D, active against Trypanosoma cruzi, Leishmania mexicana, were found to have the highest concentration among other compounds. Moreover, it has also been shown that cyanobacterial metabolites in terms of chemical functional group (Table 1). Furthermore, 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.

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 phytochemistry requires more intensive and interdisciplinary 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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