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Review Article

Pharmaceutical applications of cyanobacteria—A review

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Abstract

Cyanobacteria are emerging as an important source of novel bioactive secondary metabolites. Recently, it has also been reported as a rich source of bioactive molecules such as apratoxins, lynbyabellin, and curacin A. Some compounds have exhibited very interesting results and successfully reached Phase II and Phase III clinical trials. Furthermore, cyanobacterial compounds hold a bright and promising future in scientific research and provide a great opportunity for new drug discovery. In 2005, a number of new technologies have led to the development of new miniaturized screens based on cell cultures, enzyme activities, and ligand receptor binding. The use of a computational method based on targeted metabolite data has provided additional insight into the ligand-based approach that employs conformational analysis of known ligands. This approach has implications for developing novel compounds for structure-based drug design. Hence, this review article mainly focuses on baseline information for promoting the use of cyanobacterial bioactive compounds as drugs for various dreadful human diseases, using the computational approach.

Keywords: bioactive compounds; computational approach; cyanobacteria; dolastatin 15; drug discovery; drug for cancer

1. Introduction

Natural products are an important source of new structures leading to drugs in all major disease areas. This issue illustrates current activities and trends in the research of natural products and drug discovery. Medicinal chemistry is the cornerstone for successful hit-to-lead exploration and further lead optimization. An increase in productivity in the drug discovery process has been achieved with the implementation of library chemistry and high throughput screening. Despite these efforts, the number of new chemical entities reaching the market has not increased. Only one drug originated from a *de novo* combinatorial chemistry approach. However, natural products remain an important source of structures contributing mostly to semisynthetic or synthetic drugs in all disease areas. Therefore, therapeutic effects of natural product-derived drugs are predominantly achieved in antibiotic therapies, oncology, and immunoregulation.[1] It is less likely to identify potent natural products against molecular targets of human diseases. Natural products are important sources of new structures, leading to drugs in all major disease areas. Recently, researchers are mainly focusing on developing new drugs from marine cyanobacteria.[2]

2. Cyanobacteria

Studies of biomedical natural products have been concentrated only on Cyanophyta (blue-green algae) and Pyrrophyta (dinoflagellates); most of the metabolites have been isolated from cyanobacteria.[3,4] Cyanobacteria have been considered a rich source of secondary metabolites with potential biotechnological applications in the pharmacological field. Lately, production of bioactive compounds with commercial and medical applications has also increased interest in studying these organisms.[5] In fact, together with the production of

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potent toxins, cyanobacteria produce many substances that are interesting in terms of their antifungal, antibiotic, and anticancerigenous activities.[6,7]

Further, cyanobacterial metabolites show interesting and exciting biological activities, including antimicrobial, immunosuppressant, anticancer, anti-HIV (human immunodeficiency virus), antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, antiviral, and antitumor activities.[8–10]

The main emphasis is given on the search of drugs for dreadful human diseases such as cancer and AIDS. In recent years, scientists from different parts of the world have discovered various drugs for the treatment of such diseases. The chemical and biological diversity of the marine environment is immeasurable, making it an extraordinary resource for the discovery of new anticancer drugs from cyanobacteria (Table 1).[15,22,24,25,47–101] This review highlights several marine natural products and their synthetic derivatives that are currently undergoing clinical evaluation as anticancer drugs.[11] The past decades have seen a dramatic increase in the number of preclinical anticancer lead compounds obtained from diverse marine species that have entered into human clinical trials.[12] Productivity in the past decades in terms of discovery of new clinical anticancer leads from diverse marine life should translate into a number of new treatments for cancer in the years to come.

3. Cyanobacterial drugs for cancer

One of the most important treatments currently available for cancer and other diseases is chemotherapy, which has limited effectiveness due to some serious life-threatening side effects and development of drug-resistant cancer cells. The therapeutic efficacy and possible side effects vary among different agents. Some drugs may have excellent efficacy but can have very serious side effects. In addition, they may have very limited supply and thus can be very expensive. However, new drug discovery is a long and expensive process. It may take as long as 15–20 years and as much as billions of dollars. It is thus worthwhile to pursue a less expensive way for the production of drugs that have been found to be effective, and to develop a new way of administration or new delivery devices to increase their efficacy and eliminate/decrease their side effects. Side effects of anticancer drugs not only reduce the efficacy of chemotherapy, but also compromise the quality of Patient's life.[13] The use of natural anticancer products, for example, cyanobacterial anticancer metabolites, may improve anticancer therapy.

Thus, cyanobacteria are promising but still unexplored natural resources offering a wealth of chemicals for the discovery of lead compounds and new drugs. Of the new antibacterial and anticancer drugs approved between 1983 and 1994, up to 80% were derived from natural products. Traditional microbial drug producers such as actinomycetes and hyphomycetes have been the focus of pharmaceutical research for decades. Due to a decrease in the rate of discovery of interesting compounds in classical source organisms, it is time to turn to cyanobacteria and exploit their potential. The biosynthetic information on the chemical structures unique to these organisms will be very valuable for finding out new anticancer agents.

4. Bioactive compounds from cyanobacteria

Cyanobacteria produce a wide variety of biomedically interesting bioactive compounds, which are described below.

4.1. Borophycin

It is obtained from *Nostoc spongiaeforme* var. *tenue*. It is a boron-containing metabolite and has been found to have effective cytotoxicity for human carcinoma.[14–16]

4.2. Borophycin-8

It is obtained from *Nostoc linckia*.[17] It is made up of two identical halves with an overall structure reminiscent of other boron-containing antibiotics. The C3 starter unit for the biosynthesis of borophycin 8 is derived from acetate and methionine, but not from propionate. Borophycin and four new cyclic hexapeptides containing no boron, tenuecyclamides A–D, were also isolated from the methanol extract of *N. spongiaeforme* var. *tenue* collected from the Volcani Center, Israel.[15]

4.3. Apratoxin A

It is a cyanobacterial secondary metabolite, known as a potent cytotoxic marine natural product. It is a derivative of the apratoxin family of cytotoxins. The mixed peptide–polyketide natural product comes from a polyketide synthase/nonribosomal peptide synthase pathway. This cytotoxin is known for inducing G1-phase cell cycle arrest and apoptosis. This natural product's activity has made it a popular target for the development of anticancer derivatives. Cyanobacterial metabolites are commonly found to be useful in cancer treatment. In particular, apratoxin A has been found to be a potent cancer cell cytotoxin. It has been found to be remarkably cytotoxic in both *in vitro* and *in vivo* studies. Although much work has been done to understand the mechanism of action of this cytotoxin, there is no definite understanding of how apratoxin A mediates antitumor activity in the cell. In addition, apratoxin A lacks necessary selectivity to become a potential antitumor agent, although numerous reports have shown differential cytotoxicity in 60 tumor cell lines.[18]

4.4. Cryptophycin

It works by attacking the tubulin microfilaments found in eukaryotic cells, thereby preventing cell division and reproduction. The main hypothesis as to why blue-green algae produce this energetically expensive compound is that it is used as a strong antifungal agent in order to prevent fungi or other types of algae from competing with the cyanophyceae for nutrients and sunlight. It has been found that the amount of

Table 1
Anticancer drugs from cyanobacteria.

S. no.	Organisms	Bioactive compounds	Function	Refs
1	*Microcystis aeruginosa*	MicroviridinToxin BE-4, siatoxin	Antibiotic, anticancer	47,48
2	Cyanobacteria *N. linckia* and *N. spongiaeforme* var. *tenue*	Borophycin (image)	Cytotoxicity against human epidermoid carcinoma (LoVo) and human colorectal adenocarcinoma activity	15
3	Cyanobacteria	Apratoxins	Inhibition of a variety of cancer cell lines	25
4	*Lyngbya majuscula*	Apratoxin A	Cancer, U2OS osteosarcoma, HT29 colon adenocarcinoma, and HeLa cervical carcinoma	25
5	*Lyngbya* sp.	Apratoxins B–C	KB oral epidermoid cancer and LoVo colon cancer	25
6	*Lyngbya majuscula* and *Lyngbya sordida*	Apratoxin D	H-460 lung cancer	49
7	*Lyngbya bouillonii*	Apratoxin E	U2OS osteosarcoma, HT29 colon adenocarcinoma, and HeLa epithelial carcinoma H-460 lung cancer	25
8	*L. bouilloni*	Apratoxins F and G	HCT-116 colorectal cancer cells	25
9	*L. majuscula*	Aurilide B	H-460 lung tumor	50
10	*L. majuscula*	Aurilide C	NCI–H460 lung tumor	50
11	*Lyngbya bouillonii*	Alotamide		51
12	*L. majuscula*	Antillatoxin		52
13	*L. majuscula*	Antillatoxin B		53
14	*L. bouillonii*	Bouillomides A–B		54,55
15	*Symploca* sp.	Belamide A	HCT-116 colon cancer	56
16	*Lyngbya* sp.	Bisebromoamide	HeLa S3 epithelial carcinoma	57
17	*Lyngbya* sp.	Biselyngbyaside	HeLa S3 epithelial carcinoma, SNB-78 central nervous system cancer, and NCI– H522 lung cancer	24
18	*Calothrix*	Calothrixin A	HeLa epithelial carcinoma	58
19	*Calothrix*	Calothrixin B	HeLa epithelial carcinoma Leukemia CEM	58
20	*L. majuscula*	Caylobolide A	HCT-116 colon tumor	22
21	*Phormidium* spp.	Caylobolide B	HT29 colorectal adenocarcinoma and HeLa cervical carcinoma	59
22	*Leptolyngbya* sp.	Coibamide A	Lung cancer NCI–H460, breast cancer MDA-MB-231, melanoma LOX IMVI, leukemia HL-60 and astrocytoma SNB75, MDA-MB-435 mammary adenocarcinoma, and SKOV3 ovarian carcinoma	60
23	*N. linckia*	Cryptophycin-1	Cytotoxicity against human tumor cell lines and human solid tumors Leukemia U937, CCRF-CEM and HL-60, colon carcinoma HT-29, GC3 and Caco-2, mammary carcinoma MCF-7 and MDA-MB-231, and cervical carcinoma HeLa	61
24	*N. spongiaeforme*	Cryptophycin-8	Greater therapeutic efficiency and lower toxicity than cryptophycin-14 *in vivo*	62
25	*Geitlerinema*	Ankaraholide A	NCI–H460 lung tumor MDA-MB-435 breast carcinoma, KB oral epidermoid cancer, and LoVo colon cancer	63
26	*Chondria* sp. Red algae	Condriamide A	Cytotoxicity	64
27	*Caulerpa* sp. Green algae	Caulerpenyne	Cytotoxicity; anticancer, antitumor, and antiproliferative activities	65
28	*Cystophora* sp. Brown algae	Meroterpenes and usneoidone	Antitumor activity	66
29	*Symploca* sp. (cyanobacterium)	Largazole	Antiproliferative activity, cancer MDA-MB-23I breast cancer and U2OS osteosarcoma A549 lung cancer and HCT-116 colorectal carcinoma	25
30	*L. bouilloni* (cyanobacterium)	Apratoxin A	Cytotoxicity to adenocarcinoma	67
31	*Leptolyngbya* sp. (cyanobacterium)	Coibamide A	Cytotoxicity against NCI–H460 lung and mouse neuro-2a cells	66
32	*Nostoc* sp. GSV 224	Cryptophycin-1 Cryptophycin-52 (LY 355073) Analog of cryptophycin-52	Adriamycin-resistant M 17 breast cancer and DMS 273 lung cancer cell lines	68
33	*L. majuscule* (cyanobacterium)	Curacin A	Inhibits microtubule assembly	69
34	*Symploca* sp. (cyanobacterium)	Dolastatin 10	Binds to tubulin on rhizoxin-binding site, and affects microtubule assembly	70

(*continued on next page*)

Table 1 (*continued*)

S. no.	Organisms	Bioactive compounds	Function	Refs
35	*Symploca* sp. (cyanobacterium)	TZT-1027 analog of dolastatin 10	Effective against MX-1 breast carcinoma and LX-1 lung carcinoma in both p53 normal and mutant cells	70
36	*Leptolyngbya* sp.	Dolastatin 12	A549 lung carcinoma	71
37	*Lyngbya* sp. (cyanobacterium)	Dolastatin 15	Breast cancers (binds directly to vinca alkaloid site of tubulin)	72
38	*Lyngbya* sp. (cyanobacterium)	Cematodin (LU-103793) Analog of dolastatin 15	Breast cancers (binds directly to vinca alkaloid site of tubulin)	72
39	*Lyngbya* sp.	ILX-651 (synthadotin) Analog of dolastatin 15	Breast cancers (binds directly to vinca alkaloid site of tubulin)	72
40	*Lyngbya* sp.	Apratoxin A	Early-stage adenocarcinoma (induces G1-phase cell cycle arrest)	73
41	*L. majuscula*	Dragonamide	A-549 lung epithelial adenocarcinoma, HT-29 colon adenocarcinoma, and MEL-28 melanoma	74
42	*Oscillatoria margaritifera*	Ethyl tumonoate A	H-460 lung cancer	75
43	*Lyngbya confervoides*	Grassystatin A–B	Lung cancer	76
44	*L. majuscula*	Hectochlorin	Lung cancer	77
45	*L. majuscula*	Hermitamides A–B	Lung cancer	78
46	Assemblage of *L. majuscule* and *Phormidium gracile*	Hoiamide A	H-460 lung cancer	79
47	Cyanobacterial sample	Hoiamide B	H-460 lung cancer	80
48	*L. majuscula*	Homodolastatin 16	WHCO1 and WHCO6 esophageal cancer, and ME180 cervical cancer	81
49	*L. majuscula*	Isomalyngamide A and A-1	Breast cancer MCF-7 and MDA-MB-231	69
50	*L. majuscula*	Jamaicamides A–C nil	H-460 lung cancer	82
51	*L. majuscula*	Kalkitoxin	HCT-116 colon cancer	83
52	*Lyngbya* sp.	Kempopeptin A	Colon cancer	84
53	*Lyngbya* sp.	Kempopeptin B	Colon cancer	84
54	*L. majuscula*	Lagunamide C	Lung adenocarcinoma A549, cancer prostate PC3, ileocecal colorectal cancer HCT8, and ovary cancer SK-OV	85
55	*L. confervoides*	Largamides A–C	Cancer	86
56	*Oscillatoria* sp.	Largamides D–G	Cancer	86
57	*L. majuscula*	Lyngbyabellin A	KB nasopharyngeal carcinoma and LoVo colon adenocarcinoma	70
58	*L. majuscula*	Lyngbyabellin B	Cancer	87
59	*Lyngbya* sp.	Lyngbyaloside	KB nasopharyngeal carcinoma and LoVo colon adenocarcinoma	70
60	*L. majuscula*	Lyngbyastatin 1	Lung cancer	71
61	*L. confervoides*	Lyngbyastatin 4	Lung cancer	87
62	*Lyngbya* spp.	Lyngbyastatin 5–7	Lung cancer	79
63	*Lyngbya semiplena*	Lyngbyastatin 8–10	Lung cancer	88
64	*L. majuscula*	Majusculamide C	Lung cancer NCI–H460, colorectal cancer KM20L2, and glioblastoma SF-295	89
65	*Symploca hydnoides*	Malevamide D	Lung cancer A-549, colon cancer HT-29, and melanoma MEL-28	90
66	*Symploca laete-viridis*	Malevamide E	—	90
67	*Dichothrix utahensis*	Molassamide	—	90
68	*L. sordida*	Malyngamide 2	H-460 lung cancer	45
69	*L. majuscula*	Malyngamide C, J, and K	H-460 lung cancer	91
70	*L. majuscula*	Malyngolide dimmer	H-460 lung cancer	91
71	*Nostoc* sp.	Nostocyclopeptides A1 and A2	KB oral epidermoid cancer and LoVo colon cancer	92
72	*L. confervoides*	Obyanamide	KB oral epidermoid cancer and LoVo colon cancer	92
74	*Lyngbya* sp.	Palauamide	Cervical carcinoma HeLa, lung adenocarcinoma A549, and gastrocarcinoma BGC KB oral epidermoid cancer	92
75	*L. majuscula*	Palmyramide A	H-460 lung cancer	93
76	Assemblage of *Leptolyngbya* cf. and *Oscillatoria* spp.	Palmyrolide	H-460 lung cancer	93
77	*L. majuscule*	Pitipeptolides A–B	LoVo colon cancer	94,95
78	*L. majuscule*	Pitipeptolide C	HT29 colon adenocarcinoma and MCF-7 breast cancer	96
79	*L. majuscule*	Pitiprolamide	HCT116 colorectal carcinoma and MCF7 breast adenocarcinoma	97
80	*L. confervoides*	Pompanopeptin A	Carcinoma	86
81	*L. majuscule*	Pseudodysidenin	A-549 lung adenocarcinoma, HT-29 colon adenocarcinoma, and MEL-28 melanoma	98
82	*Symploca* sp.	Symplocamide	H-460 lung cancer	84
83	*S. hydnoides*	Symplostatin 1	MDA-MB-435 breast carcinoma and NCI/ADR ovarian carcinoma Epidermoid carcinoma cell line	90

Table 1 (*continued*)

S. no.	Organisms	Bioactive compounds	Function	Refs
84	*Symploca* sp.	Symplostatin 3	Epidermoid carcinoma cell line	70
85	*Symploca* sp.	Tasiamide	KB oral epidermoid cancer and LoVo colon cancer	84
86	*Symploca* sp.	Tasiamide B	KB oral epidermoid cancer	99
87	*Symploca* sp.	Tasipeptins A–B	KB oral epidermoid cancer	84
88	*L. confervoides*	Tiglicamides A–C C-nil	Epidermoid cancer	86
89	*Lyngbya* sp.	Ulongapeptin	KB oral epidermoid cancer	99
90	*S.* cf. *hydnoides*	Veraguamides A–G	H-460 lung cancer	100
91	*L. sordida*	Wewakazole	H-460 lung cancer	101
92	*L. semiplena*	Wewakpeptins	H-460 lung cancer	100
93	*L. majuscule* *Schizothrix* sp. assemblage	Somocystinamide A	Cytotoxic against mouse neuro-2a neuroblastoma cells	46,101

cryptophycin being produced by any one alga at any given time depends on the current environmental conditions. The recognizing property of cryptophycin allows it to recognize cancerous tumor cells, even those of "solid tumors" such as brain, colon, ovarian, prostate, pancreas, lung, and breast cancers, and it can destroy the cells of multidrug-resistant tumors. These are the cancers that chemotherapy has the least ability to treat and account for 85% of all cancer deaths in the United States.[19] Cryptophycin is now being tested in Phase I human clinical trials, and attempts have been made to create synthetic cryptophycin analogs in the laboratory to be used for further human clinical trials. Cryptophycin-1 obtained from *Nostoc* sp. has potent cytotoxic activity against human tumor cells, especially solid tumors.[20]

4.5. Cryptophycin-5

It is a chemical analog of cryptophycin-1, which entered into a clinical trial but produced only marginal activity.[21] Two other analogs, cryptophycins 249 and 309, with improved stability and water solubility are being considered as second-generation clinical candidates.[22] The enhanced efficacy of these compounds compared with that of cryptophycin-52 has prompted new efforts to move these compounds into clinical trials.

4.6. Cryptophycin-8

In the studies reported, cryptophycin-8 was evaluated for preclinical activity against subcutaneous tumors of both mouse and human origins. Cryptophycin-8 was less potent than cryptophycin-1 by approximately four-fold; however, it was more water soluble and had greater therapeutic efficacy.[23] Microalgae, notably *Dunaliella* and *Spirulina*, are also rich sources of natural beta carotene (precursor of vitamin A) and have been tested extensively for anticancer effects. Besides beta carotene, a cyanophycean algal pigment, cryptophycin, has demonstrated a powerful anticancer property that is especially useful in the chemotherapy of drug-resistant tumors.

4.7. Stypoldione

It is a marine natural product that possesses an antiquinone functional group, which inhibits a variety of biological processes including cell division. Medina et al[24] reported that stypoldione binds covalently to sulfhydryl groups of thiol-containing compounds via the addition of sulfur to the C-4′ position of the quinone ring. They examined the ability of stypoldione to add to sulfhydryl groups of a number of thiol-containing substances, including glutathione, thiophenol, beta-mercaptoethanol, and the protein tubulin.

4.8. Largazole

Largazole, a cyclic depsipeptide obtained from a cyanobacterium of the genus *Symploca*, is a marine natural product with a novel chemical scaffold and potently inhibits Class I histone deacetylases (HDACs). It possesses highly differential growth-inhibitory activity, preferentially targeting transformed cells over nontransformed cells. The intriguing structure and biological activity of largazole have attracted strong interest from the synthetic chemistry community to establish synthetic routes to largazole and to investigate its potential as a cancer therapeutic. Hence, recent advances have a focus on the discovery, synthesis, target identification, structure–activity relationships, HDAC8–largazole thiol crystal structure, and biological studies, including *in vivo* anticancer and osteogenic activities.[25]

4.9. Dolastatin 10

It was originally isolated in a very low quantity from the sea hare *Dolabella auricularia*, and it is actually a cyanobacterial metabolite, as confirmed by its direct isolation from a *Symploca* sp.[26] It is a pentapeptide containing four unique amino acids—dolavaline, dolaisoleucine, dolaproline, and dolaphenine. It is a potent antiproliferative agent. It binds to tubulin on the rhizoxin-binding site and affects microtubule assembly arresting the cell into G2/M phase. Unfortunately, in clinical tests, its Phase II trial as a single agent was discontinued because of the development of peripheral neuropathy in 40% of patients and the lack of significant activity in patients with hormone refractory metastatic adenocarcinoma[27] and recurrent platinum-sensitive adenocarcinoma.[28] An analog of dolastatin 10, TZT-1027 (auristatin PE or soblidotin), which differs from dolastatin 10 only in the absence of the thiazoline ring from the dolaphenine residue, was found to be effective in

two human xenograft models, MX-1 breast carcinoma and LX-1 lung carcinoma in mice.[29] It showed equivalent efficacy against both p53 normal and mutant cell lines,[30,31] demonstrating that a conjugate of auristatin with a monoclonal antibody directed to the adhesion molecule E-selectin can inhibit the growth of prostate cancer cells.

4.10. Dolastatin 15

Another member of the dolastatin family, dolastatin 15, is a linear peptide acting against various cancer cell lines. It binds directly to the vinca alkaloid site on tubulin and blocks the transition into M phase. No clinical trials have been undertaken with this compound because of its structural complexity, low synthetic yield, and poor water solubility. Cematodin (LU-103793), a water-soluble analog of dolastatin 15, which has a terminal benzylamine moiety in place of dolapyrolidone, retains high cytotoxicity *in vitro*. It was found to be effective in a Phase I trial for treatment of breast and other cancers by BASF Pharma (Varanasi, India), but a Phase II trial was discontinued following unexpected results. Currently, ILX-651 (synthadotin), a third-generation analog with a terminal tert-butyl moiety in place of dolapyrolidone, has successfully passed Phase I clinical trial, and a Phase II trial has been recommended.[32]

4.11. Calothrixin A

Cell extracts of *Calothrix* isolates were found to be helpful in inhibiting the growth of human HeLa cancer cells in a dose-dependent manner. Calothrixin A and B, pentacyclic metabolites, are obtained from microalgae, which have growth inhibitory effects. More than 50% of the marine cyanobacteria are potentially exploitable for extracting bioactive substances that are effective in either killing the cancer cells by inducing apoptotic death or affecting the cell signaling through activation of the members of protein kinase-c family of signaling enzymes. Cell extracts of *Calothrix* isolates inhibit the growth *in vitro* of a chloroquine-resistant strain of the malarial parasite *Plasmodium falciparum* and of human HeLa cancer cells in a dose-dependent manner. Bioassay-directed fractions of the extracts have led to their isolation and structural characterization of calothrixin A and B, pentacyclic metabolites with indole phenanthridine alkaloids, which exert their growth inhibitory effects at nanomolar concentrations.[33]

4.12. Symplocin A

Symplocin A is a new N,N-dimethyl-terminated peptide extracted from the Bahamian cyanobacterium *Symploca* sp. The complete absolute configuration of symplocin A, including the unexpected D configurations of the terminal N,N-dimethylisoleucine and valic acid residues, was assigned by chiral-phase high-performance liquid chromatography of the corresponding 2-naphthacyl esters, a highly sensitive, complementary strategy for assignment of N-blocked peptide residues where Marfey's method is ineffectual or other methods fall short. Symplocin A exhibits potent activity as an inhibitor of cathepsin E.[34]

4.13. Lyngbyatoxin A

Lyngbyatoxin A and debromoaplysiatoxin are two highly inflammatory but structurally different metabolites isolated from the toxic strains of *Lyngbya majuscula* collected from Hawaii,[35] and anatoxin-a from *Anabaena ciecinalis*.[36] Some anti-HIV activities have been observed with the compounds extracted from *Lyngbya lagerhaimanii* and *Phormidium tenue*.[37,38]

4.14. Microcolin A

An immunosuppressive linear peptide microcolin A, at nanomolar concentrations, suppresses the two-way murine-mixed lymphocyte reaction. It was isolated from *L. majusculata*.[39]

4.15. Curacin A

A unique thiozoline-containing compound, curacin A, has been purified from the organic extract of a Curacao collection of *L. majusculata*.[40] This compound has been found to have potential activity against breast cancer.[41]

4.16. Cyanobacterial drugs for AIDS

The global spread of deadly viral diseases such as HIV-acquired immune deficiency syndrome and dengue may have dramatic consequences. New potent and safe antiviral agents are urgently needed in this situation. Presently, the only approved anti-HIV treatment (highly active antiretroviral tritherapy), which is effective in controlling the progression of HIV infections, has been proved to be toxic, to induce strong viral resistance, and to be unable to eradicate the causative viral agent.[42] The following are the three classes of cyanobacterial compounds with potent *in vitro* antiviral activity. The most significant antiviral cancer polysaccharides are spirulan and Ca-spirulan from *Spirulina* sp. These compounds showed potent and broad-spectrum activity against HIV-1, HIV-2, H, influenza, and a series of other enveloped viruses. They inhibit the reverse transcriptase activity of HIV-1 (like azidothymidine). These sulfated polysaccharides prevent virus–cell attachment and fusion with host cells. They also inhibit the fusion between HIV-infected and HIV-uninfected CD4+ lymphocytes, a mechanism that greatly enhances viral infectivity. These compounds have advantages as antiviral agents over other sulfated polysaccharides because of reduced anticoagulant properties.[43] Nostoflan, an acidic polysaccharide from *Nostoc flagelliforme* that exhibits potent virucidal activity against herpes simplex virus-1, is also noteworthy. Currently, two carbohydrate-binding proteins, namely, cyanovirin-N and scytovirin, are being developed as potent virucidal drugs. These carbohydrate-binding proteins show

antiviral activity by interfering with multiple steps in the viral fusion process.

4.17. Cyanovirin-N

It is a 101-amino-acid-long, 11 kDa polypeptide isolated from *Nostoc ellipsosporum*, showing potent *in vitro* and *in vivo* activities against HIV and other lentiviruses in nanomolar concentrations. It interferes with the binding of HIV gp120 proteins with CD4+ receptors and the chemokine CCR5 or CXCR4 coreceptors of target cells, and, thus, inhibits fusion of HIV virus with CD4 cell membrane. It also inhibits herpes simplex virus-6 and measles virus *in vitro.*

4.18. Scytovirin

It is a 95-amino-acid-long, 9.7 kDa polypeptide containing five intrachain disulfide bonds. It was first isolated from the aqueous extract of *Scytonema varium*. It binds to the envelope glycoprotein of HIV (gp120, gp160, and gp41) and inactivates the virus in low nanomolar concentrations. A nuclear magnetic resonance analysis has revealed that scytovirin has two domains and the first domain (1−48 amino acids) has similar anti-HIV activity to that of the full-length scytovirin.[44] In addition, two cyclic depsipeptides, ichthyopeptins A and B, were also isolated from *Microcystis ichthyoblabe*. They have shown antiviral activity against influenza A virus.

5. Conclusion

Cyanobacteria constitute a unique group of oxygenic photosynthetic bacteria and populate diverse habitats throughout the world. Their potential as a good source of new therapeutic lead compounds has been realized during the past two decades, as several bioactive molecules obtained from cyanobacteria show a broad spectrum of activities, such as antitumor, antibacterial, and antiviral effects, and protease inhibition. Another advantage of cyanobacteria as a microbial source for drug discovery lies in the economy of their cultivation compared with other microorganisms, as the former require only simple inorganic nutrients for growth. Thus, it seems that the cyanobacteria have the potential for expanded utilization in drug discovery. Further, owing to a high degree of microbial diversity, cyanobacterial secondary metabolites may constitute a prolific source of new entities leading to the development of new pharmaceuticals.[45] Yet, exploitation of the cyanophycean species has been hampered by a number of issues related to their handling. With most of these problems having been resolved now, cyanobacteria have the potential to expand the variety of natural products obtained from microorganisms. The relative disregard of cyanobacteria in the past compared with other microbial sources of natural products, as well as the huge chemical diversity and biological activities of their products, has made them attractive sources of novel drugs for use in diverse therapeutic areas.[46] Hence, pharmaceutical potential of cyanobacteria deserves more scientific attention and interdisciplinary research, and cyanobacterial strains from still unexplored and extreme habitats can serve as good candidates in this regard.

Conflicts of interest

The authors have no conflicts of interest.

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