Cyanobacteria As A Source Of Bioactive Compounds With Anticancer, Antibacterial, Antifungal, And Antiviral Activities: A Review

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Abstract

Cyanobacteria a group of photosynthetic microorganisms, exist in almost all ecosystems in the world. Regarding health and disease prevention, cyanobacteria have been cited as a promising natural source of diverse secondary metabolites that exhibit significant bioactivities with potential pharmacological uses. Presently, great attention has been concentrated on the anticancer role of aquatic cyanobacteria that comprise an important source of bioactive compounds. Cyanobacteria-derived natural compounds and their synthetic analogs exhibited attractive results and showed remarkable activity by reaching phase II and III clinical trials successfully. Therefore, natural products from cyanobacteria might represent promising sources for novel anticancer therapy. Besides, microbial infections and infectious diseases from antimicrobial resistance (AMR) pose a direct threat to health and well-being because of the increase in antimicrobial resistance and the evolution of novel pathogenic strains. The search for novel antibiotics become increasingly urgent. Extensive efforts have been invested to find antimicrobial compounds from cyanobacteria to limit the misuse of commercial antibiotics. The development of natural anticancer and antimicrobial compounds from fresh water and marine cyanobacterial metabolites is a valuable trial. This review article summarizes the reported anticancer, antiviral, antifungal, and antibacterial properties of cyanobacteria and their mechanisms of action.

Keywords: Anticancer; Antimicrobial; Bioactive compound; Cyanobacteria-novel therapies for their effective use in clinical practice and to improve patient-related outcomes.

Significance | Various important bioactivities possessed by cyanobacteria and their mechanism of actions were described in this review article, with emphasis on anticancer potential.

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1 Introduction

Cancer presents the second most deadly disease in the world. sNigam et al., 2019). The WHO revealed that, in 2018, cancer was responsible for about 10 million deaths, and nearly 1 out of 6 deaths in the world (Damodaran et al., 2019). In 2021, around 1.9 new cancer cases and more than 608,000 cancer deaths were reported in the USA (Siegel et al., 2021). Environmental factors including smoking, radiation, infection, diet, stress, and environmental pollution cause approximately 90-95% of cancer cases, while 5-10% are caused by genetic defects (Pumiputavon et al., 2017). Cancer is mostly managed by conventional tumor therapies such as surgical removal, chemotherapy, and radiotherapy. These therapies cause many serious drawbacks (Osman et al., 2020). To overcome the problems of the present therapies, it has been a concern for many researchers to find out

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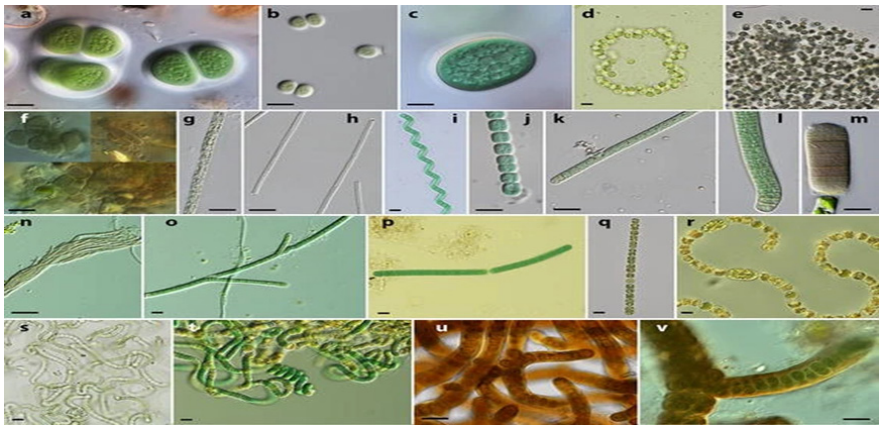

Figure 1. Morphological diversity of cyanobacteria (Dvořák et al., 2015)

new anticancer drugs with increased efficiency and limited detrimental side effects on the immune system and the general health of the patient (Ferdous and Yusof, 2021). On the other hand, antimicrobial resistance (AMR) has become one of the most significant threats to human health across the globe. AMR occurs when pathogenic bacteria, fungi, and viruses continue to grow and replicate in the presence of drugs that once affected them. The Centers for Disease Control and Prevention (CDC) reported that around 2 million cases of AMR diseases occur every year in the USA, and more than 23,000 deaths. AMR infections cause serious illness and lead to extended hospital admissions, and raise the costs of healthcare. Whereas, in Europe, due to the common AMR bacteria (*Klebsiella pneumonia, S. aureus, Streptococcus pneumoniae, Escherichia coli,* and *Pseudomonas aeruginosa*) the infections number was approximately 400,000 cases, around 25,000 deaths, in 2007 (Prestinaci, et al., 2015). In addition, more than 9 billion euros have been spent on AMR diseases every year. Currently, *Staphylococcus aureus* resistance to Methicillin is a well-known case of AMR, related to a high rate of mortality every year worldwide (Dadgostar, 2019). In addition, pathogenic fungi have shown resistance toward many antifungal medications (Swain et al., 2017). Moreover, the available medicines are efficient for only one-third of human diseases due to the increased antibiotic resistance to pathogens. The pharmaceutical industry spent about 868 million dollars to bring novel medicine to the markets (Adams and Brantner, 2006). Accordingly, there is a shortage supply of novel therapeutic medicines reaching the global markets. Therefore, the identification of novel bioactive compounds has been required urgently to develop novel medicines. Natural products have an essential role in terms of developing drugs in all major therapeutic areas (Swain et al., 2017). It has been estimated that about 70% of medicines approved for clinical use are produced from natural products (Rao et al., 2007), and 60% of approved anticancer drugs are synthesized from natural origin (Boopathy and Kathiresan, 2010). The unique secondary metabolites arise from cyanobacteria with diverse biological activities and a broad range of chemical classes that have the capability for expansion of the pharmaceuticals and medical applications (Nowruzi et al., 2019). A new study demonstrated that the chemical diversity of natural products from cyanobacteria exceeds around 1100 natural compounds, two to thirds of them are obtained from *Microcystis* sp., *Lyngbya* sp., and *Hapalosiphon* sp. These molecules with diverse structures have promising therapeutic including antibacterial, anticancer, anti-inflammatory, antiviral, enzyme-inhibiting bioactivities, and antifungal (Gkelis et al., 2019). Nowadays, molecules with potential anticancer activity have been purified from cyanobacteria, for example, curacin A, is purified from *Lyngbya majuscula* and showed anticancer activity toward various cancerous cells including colon cancer, breast cancer, and renal cancer cell lines (Zanchett and Oliveira-Filho, 2013). Another example, calothrixin A, purified from *Calothrix* sp. showed activity against HeLa cervix adenocarcinoma cells (Chen et al., 2003). Cryptophycin-52 lead to acting as an anticancer agent against human prostate cancer cells via inducing apoptosis in various pathways including activation of caspase-1 and caspase-3 and phosphorylation Bcl-xL and Bcl-2 (Aesoy and Herfindal, 2022). Cyanobacteria have been found to produce a broad spectrum of secondary metabolites that induced apoptotic (Costa et al., 2012). Apoptosis is one of the most effective strategies to kill tumor cells. This process involves various signaling pathways and results in a multitude of changes in the dying cells (Osman et al., 2020). The mechanism of apoptosis has been related to many crucial regulators including the induce of cell cycle arrest, activation of caspase cascade, alteration in Bcl-2 protein family, or mitochondrial dysfunctions (Costa et al., 2012). Besides, secondary metabolites with potential antibacterial activity are widely produced by cyanobacteria (Pandy, 2015). It has been found that

Table 1. Cyanobacterial secondary metabolites with anticancer activity

Bioactive compound	Source	Activity	Reference
Apratoxin A	*Lyngbya majuscula*	Activation of caspase-3 and -7 in osteosarcoma (U2OS) cells	Luesch et al., 2006
Apratoxins B	*Lyngbya* sp.	KB oral epidermoid cancer and LoVo colon cancer	Mondal et al., 2020
Apratoxins C	*Symploca cf. sp.*	Cytotoxic on various cancer cell lines	Mondal et al., 2020
Apratoxin D	*Lyngbya majuscula*	NCI-H460 lung cancer	Qamar et al., 2021
Apratoxin E	*Lyngbya bouilloni*	Cytotoxic on cervix, colon, and bone cancer cells	Matthew et al., 2008
Calothrixin B	*Calothrix* sp.	(HCT-116) colon cancer	Hatae et al., 2014
Oxadiazinenocuolin	*Nostoc* sp. and *Anabaena* sp.	Caspase activation in HeLa cells	Voráčová et al., 2017
Coibamide A	*Leptolyngbya* sp.	Exhibit significant activities on Leukemia HL-60, (LOXIMVI) human melanoma, and human breast cancer cells	Serrill et al., 2016
Largazole	*Symploca* sp.	Antiproliferative activity in cancer	Hong and Luesch, 2012
Condriamide A	*Chondria* sp.	Cytotoxic against KB cells and LOVO cells	Khalifa et al., 2019
Pitipeptolides A-B	*Lyngbya majuscula*	LoVo colon cancer	Luesch et al., 2001
Bisebromoamide	*Lyngbya* sp.	HeLa (S3) epithelial carcinoma	Robles-Bañuelos et al., 2022
Malyngolide dimmer	*Lyngbya majuscula*	Inhibit (H-460) lung cancer	Gutierrez et al., 2010
Hermitamides A-B	*Lyngbya majuscula*	Cytotoxic against lung cancer cells	De Oliveira et al., 2011
Tolyporphin	*Tolypohrix nodosa*	Cytotoxic against (EMT-6) tumor cells in mice	Morlière et al., 1998
Somocystinamide A	*Lyngbya majuscula*	Induce apoptosis in Jurkat cell, (A549) lung carcinoma, and NB7 neuroblastoma	Wrasidlo et al., 2008
Hectochlorin	*Lyngbya* sp.	Inhibit cell cycle in Burkitt lymphoma	Ercolano et al., 2019
Kanamienamide	*Moorea bouilloni*	Growth inhibitory in HeLa cancer cells	Sumimoto et al., 2016
Langunamide A, B, C	*Lyngbya majuscula*	Cytotoxic against (HCT8) colon cancer, (A549) lung carcinoma and PC3 cancer prostate	Tripathi et al., 2012
Aurilide B	*Lyngbya majuscula*	Cytotoxic against H-460 lung cancer	Han et al., 2006
Aurilide C	*Lyngbya majuscula*	Cytotoxic against NCI-H460 lung tumor	Han et al., 2006
Hantupeptin A	*Lyngbya majuscula*	Cytotoxic against MOLT-4 leukemia and MCF-7 adenocarcinoma breast cancer cells	Tan, 2007
Grassystatin A-B	*Lyngbya confervoides*	Lung cancer cells	Kwan et al., 2009
Homodolastatin 16	*Lyngbya majuscula*	ME180 cervical cancer cells	Davies-Coleman et al., 2003
Carmaphycin A and B	*Symploca sp.*	Cytotoxic against HCT-116 colon cancer and NCI-H460 human lung adenocarcinoma	Robles-Bañuelos et al., 2022
Borophycin	*Nostoc linckia*	Cytotoxic against KB cells and LOVO cells	Hemscheidt et al., 1994
Jamaicamides A-C	*Lyngbya majuscula*	NCI-H460 lung cancer cells	Edwards et al., 2004
Symplocamide	*Symploca* sp.	NCI-H460 lung cancer and neuroblastoma	Tan, 2010
Symplostatin 3	*Symploca* sp.	Cytotoxic against KB cells and LoVo cells	Kumla et al., 2022
Kempopeptin A-B	*Lyngbya majuscula*	Colon cancer cells	Taori et al., 2008
Pitiprolamide	*Lyngbya majuscula*	Breast adenocarcinoma and colorectal carcinoma	Montaser et al., 2011
Tasiamide	*Symploca* sp.	KB oral epidermoid and LoVo colon cancer	Williams et al., 2002
Ulongapeptin	*Lyngbya* sp.	KB oral epidermoid cancer	Williams et al., 2003
Majusculamide C	*Lyngbya majuscula*	Colorectal cancer, lung cancer, glioblastoma, and ovarian carcinoma	Kang et al., 2018
Ankaraholide A	*Symploca sp.*	NCI-H460 lung cancer cells, MDA-MB-435 human breast cancer	Andrianasolo et al., 2005
Hoiamide A	*Lyngbya majuscula* and *Phomidium gracile*	H460 lung cancer	Zhang et al., 2013
Hoiamide B	Cyanobacteria	H460 lung cancer	Zhang et al., 2013
Malevamide D	*Symploca hydnoides*	HT-colon cancer and A-549 lung cancer	Horgen et al., 2002
Malyngamide 2	*Lyngbya Sordida*	H-460 lung cancer	Malloy et al., 2011
Palaumide	*Lyngbya majuscula*	A-549 lung cancer and HeLa cervical carcinoma	Zou et al., 2005
Isomalyngamide A	*Lyngbya majuscula*	MDA-MB231 and MCF-7 breast cancer	Shih et al., 2020
Biselyngbyaside	*Lyngbya* sp.	SNB78 central nervous system cancer, HeLa S3	Teruya et al., 2009

Anaenamides A-D	*Hormoscilla sp.*	Cytotoxic against HCT-116 colon cancer cells	Benjamín Robles-Bañuelos et al., 2022
Lyngbyastatin 4	*Lyngbya confervoides*	Inhibits bovine pancreatic chymotrypsin and porcine pancreatic elastase	Matthew et al., 2007
Tiglicamides A-C	*Lyngbya confervoides*	Porcine pancreatic elastase	Matthew et al., 2009

Table 2. Cyanobacterial compounds approved/clinical trials as anticancer drugs

Clinical status	**Compound name**	**Source**	**Activity**	**Reference**
Approved	Brentuximab vedotin,	*Symploca* sp.	Hodgkin's lymphoma treatment	Robles-Bañuelos et al., 2022
Phase III	Soblidotin (TZT-1027)	*Dolabella auricularia* and cyanobacteria	Human colon adenocarcinomas	Mondal et al., 2020
Phase II	Tisotumab Vedotin	Cyanobacteria	Solid tumors including cervical cancer	Nigam et al., 2019
Phase II	Glembatumumab vedotin	Cyanobacteria	Melanoma and breast cancer	Ott et al., 2017
Phase II	Synthadotin, (ILX-651)	Cyanobacteria	Metastatic melanoma	Mondal et al., 2020
Phase I	Pinatuzumab vedotin	Cyanobacteria	Inhibit leukemia and Non-Hodgkin lymphoma	Advani et al., 2017

Table 3. Cyanobacterial secondary metabolites with antibacterial activity

Bioactive compound	**Source**	**Specific class**	**Activity**	**Reference**
Ambiguine I isonitrile	*Fischrella sp.*	Indol alkaloid	*Staphyloccocus abus, M.tuberculosis, Bacillus subtilis, E. coli ESS K-12*	Raveh and Carmeli, 2007; Mo et al., 2009
Carbamidocyclophanes	*Nostoc sp.*	Cyclophane	*Staphylococcus aureus*	Preisitsch et al., 2015
Cariolic acid	*Oscillatoria redekei*	Fatty acid	*B. subtilis SBUG 14, Micrococcus flavus*	Mundt et al., 2003
Eucapsitrione	*Fischerella ambigua*	Alkaloid	*Staphylococcus aureus*	Sturdy et al., 2010
Hapalindole T	*Fischerella sp.*	Indole alkaloid	*Staphylococcus aureus*	Asthana et al., 2006
Noscomin	*Nostoc commune*	Diterpenoid	*M. tuberculosis*	Jaki et al., 2000
Lyngbyazothrins A,B	*Lyngbya sp.*	Cyclic undecapeptides	*Bacillus cereus, E.coli, Staphylococcus epidermidis*	Rojas et al., 2020
Lyngbyazothrins C,D	*Lyngbya sp.*	Cyclic undecapeptides	*Micrococcus flavus, E. coli, Serratia marcescens, Pseudomonas aeruginosa*	Rojas et al., 2020
Pitipeptolides A,B	*Lyngbya majuscula*	Cyclic depsipeptide	*M. tuberculosis*	Luesch et al., 2001
Pahayokolide A	*Lyngbya sp.*	Cyclic peptide	*Bacillus sp.*	Berry et al., 2004

these compounds are efficient toward many types of microorganisms (Abed et al., 2008). For example, in 1979, malyngolide purified from cyanobacteria is the first polyketide antibiotic that can inhibit the growth of both Gram-positive and Gram-negative pathogenic strains including *Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis*, *Pseudomonas aeruginosa* and *Chromobacterium violaceum* (Cardllina et al., 1979; Dobretsov et al., 2010). In addition, the peptides, kawaguchipeptins A and B, obtained from *Microcystis aeruginosa*, are active on *Staphyloccocus aureus.* The pitipeptolides A-F, extracted from *Lyngbya majuscula* showed activity on *Mycobacterium tubercolosis* (Carpine et al., 2021). Furthermore, diterpenoid noscomin, purified from cyanobacterium *Nostoc commune,* showed activity on *Escherichia coli* and *Staphylococcus epidermidis* (Kar et al., 2022). Besides, hassallidins are lipopeptides, obtained from cyanobacterium *Hassallia* sp. and *Anabaena* sp have potential fungicidal effects on many opportunistic human pathogenic fungi as example *Aspergillus flavus* and *Candida albicans* (Shishido et al., 2015, Humisto et al, 2019). Consequently, Ca-Sp is a sulfated polysaccharide, purified from *Spirulina platensis*, which has antiviral activity against a series of enveloped viruses that include human cytomegalovirus (HVMV), mumps virus, HIV, measles virus, and influenza virus (Tiwari and Tiwari, 2020). Thus, AMR infections can be managed by discovering new medications, and cyanobacterial molecules could be potential candidates (Kar et al., 2022). In this review, we highlight some aquatic cyanobacterial metabolites which showed strong effects on cancer cell lines, and some of them have been entered into human clinical trials. Moreover, it focuses on cyanobacterial bioactive compounds which have potential antiviral, antifungal, and antibacterial activities against a wide range of microorganisms.

2 Cyanobacteria

Cyanobacteria (blue-green algae) is a group of photosynthetic Gram-negative prokaryotes, consider one of the oldest microorganisms on the planet Earth, with a fossil record of 2000–3500 million years (Zanchett and Oliveira-Filho, 2013). These prokaryote organisms are termed cyanophytes, cyanoprokaryotes, and blue-green algae. Cyanobacteria exist in environments in different morphologies such as unicellular, colonial, ranched filamentous, and unbranched filamentous with trichomes, as shown in Figure 1 (Dvořák et al., 2015). These microorganisms occur in diverse environments, from aquatic (freshwater and marine) to terrestrial, and they can inhabit in different extreme environments such as high salinity, geothermal springs, and deserts (Nandagopal et al., 2021). These microorganisms can effectively thrive and compete in nature because of the high degree of biological adaptation (Dewi et al., 2018).

Basically, cyanobacteria produce two types of metabolites, primary metabolites including proteins, carbohydrates, lipids, and chlorophyll needed for survival, and secondary metabolites including tannins, alkaloids, carbohydrates, phenols, saponins, and flavonoids, required for defense mechanisms and stress responses (Kultschar and Llewellyn, 2018). These unique bioactive molecules with potential medical properties are produced by integrating non-ribosomal peptide synthetases with polyketide synthases, resulting in chemically various structures including fatty acid amides, linear peptides, cyclic peptides, linear lipopeptides, glicomacrolides or macrolactones (Ercolano et al., 2019). Hundreds of these compounds have been extracted and tested, and many of them possess a wide range of potent pharmacological functions for example antifungal, anti-inflammatory, antiprotozoal, immuno-suppressant, antibacterial, anticancer, anticoagulant, antimalarial, anti-tuberculosis, anti-HIV, and antiviral activities (Dixit and Suseela, 2013). Many studies reported the potential of secondary metabolites from cyanobacteria in pharmaceutical and biotechnological.

3 Cyanobacterial metabolites with anticancer activity

A broad range of natural compounds obtained from cyanobacteria exhibit cytotoxic effects and potentially kill various cancerous cells by inducing apoptosis, which are described below.

3.1 Cryptophycins

Cryptophycins are a large group of cyclic depsipeptide with potent cyanotoxins, purified from cyanobacterium *Nostoc* sp. (Polyzois et al., 2020). Cryptophycins exhibit high biological activity both in vivo and in vitro. Cryptophycin-1 activates the microtubule instability of the cell, inhibits microtubule assembly, and induces tubulin self-association, thereby leading to cell cycle arrest by inhibiting cells in the G2/M phase. This compound has been found to have excellent cytotoxic effects in low concentrations against a range of cancer cells, for example, the IC50 values on KB human nasopharyngeal cancer was 4.58 pM and 7.63 pM on LoVo human colorectal cancer (Weiss et al., 2017). Cryptophycin-52 lead to acting as an anticancer agent on prostate cancer cells by inducing apoptosis in various pathways including activation of caspase-1 and caspase-3 and phosphorylation Bcl-xL and Bcl-2. Cryptophycin-52 underwent advanced clinical trial phase II against human non-small cell lung carcinoma, but it failed due to unacceptable side effects such as neuropathy, constipation, and pain sensation (Aesoy and Herfindal, 2022). Nowadays, researchers have developed cryptophycin conjugates with antibodies and peptides to target drug delivery in cancer therapy (Qamar et al., 2021).

3.2 Dolastatin 15

It is a small linear peptide, obtained first from cyanobacterium *Symploca* sp. Dolastatin 15 has been considered a promising

anticancer agent against solid tumors and some leukemia, by acting as a mitotic inhibitor by binding to tubulin and blocking microtubule assembly. Dolastatin 15 also activates apoptosis through a simultaneous increase in Bcl-2 phosphorylation (Kapoor and Shailendra, 2013).

3.3 Curacin A

A complex ketopeptide, extracted from cyanobacterium *Lyngbya majuscula*. Curacin A has antiproliferative and antimitotic activity toward colon, breast, and renal cancer cells. This molecule was reported to arrest the cell cycle by binding to the colchicine-binding site on tubulin leading to inhibit microtubule polymerization (Zanchett and Oliveira-Filho, 2013).

3.4 C-phycocyanin (C-PC)

The blue color pigment is a member of the phycobiliprotein (PBP) family along with phycoerythrin and allophycocyanin. Phycocyanin is a photosynthetic assistant protein that can efficiently harvest light energy (Jiang et al., 2017). C-PC is involved in most of the biological activity of the cyanobacterium genus of *Spirulina* sp. Researchers have revealed that C-PC showed antiproliferative and pro-apoptotic effects against various cancerous cells for example, leukemia, colon cancer, breast cancer, and lung cancer both in vivo and in vitro, while it has not shown an effect on normal cells (Hao et al., 2018). Phycocyanin inhibits tumor cell proliferation by inducing cell cycle arrest and activating apoptotic via several mechanisms, for example, the efficiency of C-phycocyanin in breast cancer cell line MDA-MB-231 was mediated by the initiation of apoptosis via upregulation of the level of Fas protein and splitting of caspase-3, whereas Bcl-2 protein downregulation was observed (Jiang et al., 2018). Furthermore, the pro-apoptotic phycocyanin has been mediated by cytochrome c release from mitochondria into the cytosol, in leukemia cell lines (Ercolano et al., 2019). Moreover, in HeLa cervix adenocarcinoma cells, phycocyanin can promote the CD59 and Fas protein expression, while it has not shown a significant efficiency on the expression of Fas protein and CD59 in normal Chinese Hamster Ovary CHO cells (Li et al., 2005).

3.5 Calothrixin A

Is a pentacyclic indolophenanthridine, purified from cyanobacterium *Calothrix* sp. Cell cycle analysis showed that calothrixin A caused G2/M arrest against several cancer cells. This molecule has also the ability to increase intracellular (ROS), thereby leading to inducing DNA fragmentation in Jurkat Human T cell lines. In addition, in nanomolar concentrations, calothrixin A showed activity against HeLa cervix adenocarcinoma cells (Chen et al., 2003).

3.6 Symplostatin 1

A dolastatin 10 analog, purified from the genera *Symploca hydnoides*. Symplostatin 1 and dolastatin 10 have similar structures, differing only in the N terminus. Symplostatin 1 inhibits cellular proliferation with IC_{50} values in the low nanomolar range and shows effectiveness on many cancer cells including human breast carcinoma and human ovarian carcinoma cells. This molecule caused abnormal mitotic spindle formation and cell accumulation in metaphase at concentrations that showed low effects on microtubules. Symplostatin 1 affects mitotic spindles and then activates cell cycle arrest in the G2/M phase. Furthermore, this molecule initiates the formation of micronuclei, phosphorylation of Bcl-2, and activation of caspase 3, leading to induce apoptosis (Mooberry et al., 2003).

4 Approved and under clinical trials anticancer drugs from cyanobacteria

Chemotherapy is one of the most important therapeutic available for cancer treatment, which has many serious drawbacks and limited efficacy. The process to develop a novel drug is long and costly, as it may take 15-20 years and cost billions of dollars. Therefore, there is an urgent need to find alternatives with minimum side effects, less expensive, and new delivery devices to raise their effectiveness (Feng and Chien, 2003). Nowadays, several anticancer compounds isolated from cyanobacteria are undergoing clinical trials phase. These compounds regulate macromolecule expression in cancer cells by signal transduction pathways leads to induce anticancer activity (Mondal et al., 2020). Dolastatins are a group of peptides, purified from *Lyngbya* sp. and *Symploca* sp., exhibiting cytotoxic effects against several cancer cells (Mondal et al., 2020; Qamar et al., 2021). Dolastatin 10 and dolastatin 15 are members of the dolastatin family, triggering cell cycle arrest in the G2/M phase and leading to apoptosis in various cancer cells. In the 1990s, dolastatin 10 underwent advanced clinical trial phase II, but was discontinued due to dose-limiting side effects, specifically the development of peripheral neuropathy in patients. Subsequently, a group of analogs namely auristasins were developed, because of the structure–activity relationship analyses. Auristatins were designed to join a linker to ease their conjugation to monoclonal antibodies, leading to a decrease in the toxicity derived from their low selectivity. Furthermore, designing and utilizing the members of auristatin family with high-precision monoclonal antibodies to deliver the drug to antigen-positive cancer cells (Robles-Bañuelos et al., 2022). Antibody-drug conjugates (ADCs) have been developed to become one of the most promising cancer therapies because of their high efficacy and low toxicity (Wang et al., 2017). Interestingly, in August 2011, one of dolastatin 10 derivatives, a highly effective antibody-drug conjugate namely *Brentuximab vedotin* (Adcetris) has been granted FDA approval to treat Hodgkin's lymphoma (table 2) (Pereira et al., 2019).

Soblidotin (Auristatin PE) is a synthetic analog derivative of dolastatin 10, a Phase III clinical research after completing Phase I and II clinical trials, under Aska Pharmaceutical, Soblidotin causes a collapse in the vasculature of the cancer with tubulin inhibitory activity, leading to cell death (Mondal et al., 2020). Tisotumab Vedotin is an antibody-drug conjugate under Phase II of clinical research, extracted from cyanobacteria and mollusks. Tisotumab Vedotin targeted the protein involved in angiogenesis and signaling, Tissue Factor (TF), which is expressed in various solid tumors (Nigam et al., 2019). Glembatumumab vedotin is an antibody–drug conjugate that is approved for phase II clinical trials. Glembatumumab vedotin exhibits anticancer activity in melanoma and breast cancer (Ott et al., 2017). Pinatuzumab vedotin is an antibody-drug-based conjugate under Phase I of clinical trials, purified from cyanobacteria and mollusks. It is formed of monomethyl auristatin E, an antimicrotubule agent, conjugated to (CD22) antibody. Moreover, Pinatuzumab vedotin exhibited inhibitory action on chronic lymphocytic leukemia and Non-Hodgkin Lymphoma (Advani et al., 2017). Synthadotin (SYN-D; ILX651) is a synthetic analog of dolastatin 15, under phase II clinical research (table 2). It has a high-potency anticancer agent in patients with advanced-stage of metastatic melanoma since it showed low toxicity and microtubule inhibition activity. Therefore, cyanobacteria are promising natural resources presenting a rich and diverse array of bioactive molecules for the discovery of lead compounds and novel drugs.

5 Antimicrobial activity

Multidrug-resistant pathogenic bacteria, viruses, and fungi, infections are still intractable. However, the search for new antimicrobial compounds from other non-conventional against (MDR) pathogenic microorganisms is importantly required. As a background, cyanobacteria have enormous natural compounds as a source of various chemical substances with antimicrobial properties such as fatty acids, terpenes, halogenated aliphatic compounds, acrylic acid, pigments, peptides, flavonoids, vitamins, carbohydrates, sulfur-containing heterocyclic compounds, phenolic compounds, flavonoids and many other compounds with potential uses as biopharmaceuticals (Swain et al., 2017; Gheda and Ismail, 2020).

5.1 Cyanobacterial metabolites with antibacterial activity

Nowadays, bacteria resistance to antibiotics continues to rise, they have posed therapeutic challenges and become a clinical annoyance. Resistance to antibiotics has appeared in most pathogenic bacteria. Many of these bacterial species become resistant to all available antibiotics, which leads to creating an "antibiotic resistance crisis". It is expected that around 300 million premature deaths will be the human cost of this crisis, and the world economy losing will reach $100 trillion, by 2050. The effort to develop novel antibacterial compounds in the last few decades has faced countless challenges, and in many cases, failure (Alsenani et al., 2020). Thus, the high level of attention has turned to alternatives from natural sources. In the effort to develop novel antibiotics, researchers have screened the cyanobacteria-derived bioactive compounds for their antibacterial activity and they exhibited potent effects on different types of bacteria. Table 3 and the section that follows summarize numerous cyanobacterial compounds with antibacterial activity, their chemical diversity, and the producer cyanobacteria species.

Gademann and Portmann (2008) reported that scytptolin A, a depsipeptide, isolated from cyanobacterium *Scyptonema hofmanni* inhibited serine protease of bacterial cell wall biosynthesis (Gademann and Portmann, 2008). Moreover, the cyano-peptide, such as borophycin, scyptolin A, scytonemin A, kawaguchipeptin A, B, and tenuecyclamide A-D, showed activity against several pathogenic bacteria (Swain et al., 2017). In addition, 9 Hapalindole-type alkaloids, characterized by *Fisherella ambigua*, has reported to be active against *Bacillus anthrasis*, *Bacillus subtilis,* and *Staphylococcus albus* (Mo et al., 2009). Doan and coworkers (2001) demonstrated that the alkaloid, 12-epi-hapalindole E isonitrile, isolated from cyanobacterium *Fischerella* sp. inhibits the bacterial RNA polymerase (Doan et al., 2001). The indole alkaloids, ambiguine isonitriles A, K, and M, isolated from *Fischerella ambigua* were active toward *Mycobacterium tuberculosis* (Mo et al., 2009). The antibacterial activity of terscytoscalarol, a tetraterpene, obtained from *Scytonema* sp. showed potent activity on *Bacillus anthracis* and *Staphylococcus aureus* with MIC values of 1.7 μM and 6.0 μM, respectively (Mimouni et al., 2012). Volk and Furkert (2006) demonstrated that the phenol compound 4-4́-hydroxybiphenyl isolated from cyanobacterium *Nostoc insulare* has antibacterial activity (Volk and Furkert, 2006). Similarly, nostocine A, extracellular pigments, crossbyanol A-D, polyphenyl ether, polyporphin J, and porphinoid were reported to have antibacterial activities (Hirata et al., 2003; Prinsep et al., 1992). Moreover, crossbyanol B showed antibacterial activity in MRSA strain, with a MIC value 2.0 μg/ml – 3.9 μg/ml (Choi et al., 2010). The new cyanobacterial compound EMTAHDCA (9-ethyliminomethyl-12-(morpholin-4-ylmethoxy)-5,8,13,16-tetraaza-hexacene-2,3 dicarboxylic acid) isolated from *Nostoc* sp. has antibacterial activity towards some types of bacteria including *E. coli*, *Pseudomonas aeruginosa,* and *Proteus vulgaris*, by binding to their active sites on the proteins and 30S ribosomes (Niveshika et al., 2016). Consequently, some antibacterial terpenes have been isolated from cyanobacteria, such as diterpenoid noscomin, obtained from *Nostoc commune* in 1999, exhibit potent activity on *Staphylococcus epidermidis, Bacillus cereus*, and *Escherichia coli*. Scytoscalarol, is a sesterterpenes bearing a

guanidino group, purified from cyanobacterium *Scytonema*. This molecule showed activity in the low molecular range on Gram-positive bacteria and Gram-negative bacteria such as Escherichia coli (Carpine et al., 2021). These examples highlight the potential of metabolites extracted from cyanobacteria to treat pathogenic bacteria.

5.2 Cyanobacterial metabolites with antifungal activity

Since the 1990s, invasive fungal infections, especially fusariosis and aspergillosis have increased dramatically in immunocompromised patients (Yamazaki et al., 1999). Systemic fungal infection treatments are restricted to a few available classes of agents, which are related to some toxicity problems, drug resistance, and a limited spectrum of action (Shalini et al., 2011). Thus, systemic fungal infections continue to expand the urgent need for novel antifungal drugs, which should have a safe broad fungicidal spectrum of action and limited side effects. Cyanobacteria produce a broad spectrum of antifungals including polyketides, peptides, and alkaloids having future therapeutic applications (Shishido et al., 2015). Here we highlight some classes of cyanobacterial compounds that have shown antifungal activity.

5.2.2 Hassallidins

Hassallidins are cyclic glycosylated lipopeptides, isolated from epilithic cyanobacterium *Hassallia* sp. and *Anabaena* sp. (Vestola et al., 2014). The structure of Hassallidin comprises a peptide ring of eight amino acids to which a fatty acid chain, additional amino acids, and sugar moieties are attached (Humisto et al., 2019). These molecules have potential antifungal activity on several opportunistic human pathogenic fungi such as *Candida albicans* and *Aspergillus flavus* by targeting the function of cell membranes (Shishido et al., 2015, Humisto et al, 2019).

5.2.3 Lyngbyabellins

Lyngbyabellins are cyclic depsipeptides, extracted from the genera of *Lyngbya majuscula, Lyngbya bouillonii,* and *Moorea bouillonii*. *Hectochlorin* is a member of Lyngbyabellins family tested for antifungal and antibacterial activity, showed no antibacterial activity, but presented antifungal activity towards *Candida albicans*. The lyngbyabellins can disrupt actin filaments. Furthermore, treating cells with lyngbyabellin A and E, lead to induce cell cycle arrest at the cytokinesis phase due to losing their microfilament network (Luesch et al., 2000; Han et al., 2005). Marquez and co-workers (2002) reported that the same process happens when cells are exposed to hectochlorin. In addition, they showed that the molecule stimulates actin polymerization and then induces cellular cycle disorders (Marquez et al., 2002).

5.3.3 Microguanidines

Microguanidines are guanidine derivatives. They have been purified from *Microcystis* sp. (TAU IL-306) and *Microcystis aeruginosa*. Microguanidines have shown antifungal activity on Saccharomyces cerevisiae E4orf4 without showing a cytotoxic effect. This specificity could be interesting to develop novel specific antifungal drugs (Gesner-Apter and Carmeli, 2008).

Majusculamides are lipopeptides, obtained from *Lyngbya polychroa* and *Lyngbya majuscula*. Majusculamides combine cytotoxicity and antifungal activity with anti-settlement and immunosuppressive properties (Demay et al., 2019). In addition, Simmons and co-workers (2009) reported the majuscuamides ability to disrupt actin filaments that illustrate the specific properties (Simmons et al., 2009).

Furthermore, 4,4′-dihydroxybiphenyl and norharmane isolated from *Nostoc insulare* and *Nodularia harveyana* successfully inhibited the growth of *Candida albicans* with a MIC value 32 µg/ml and 40 µg/ml, respectively (Volk and Furkert, 2006). Similarly, fatty acids purified from *Synechocystis sp*. were effective against *Candida albicans* (Najdenski et al., 2013). Scytophycins purified from *Scytonema* sp., *Nostoc* sp., and *Anabaena cf. cylindrical* showed fungicidal effects on *Aspergillus flavus* and *Candida albicans* (Shishido et al., 2015). Laxaphycins A and B, are cyclic peptides purified from *Anabaena laxa* have shown antifungal activity by targeting the enzymes involved in the synthesis of cell walls (Zhang and Chen, 2022). Marrez and Sultan (2016) reported that the diethyl ether extracts *Microcystis aeruginosa* showed antifungal activity against *Penicillium verrucosum, Fusarium verticillioides, Aspergillus species,* and *Fusarium proliferatum* (Marrez and Sultan, 2016). Furthermore, Nowruzi et al. (2021) demonstrated that various cyanobacteria including *Calothrix, Nostoc, Anabaena*, and *Nodularia* can inhibit the growth of two pathogenic fungi namely *Botrytis* and *Alternaria alternata* (Nowruzi et al., 2021).

5.3 Cyanobacterial metabolites with antiviral activity

Since the 20th century, viral diseases have impacted human society due to the spread of many deadly viral diseases including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), swine influenza (H1N1), avian influenza, Ebola, and nowadays, coronavirus disease 2019 (COVID-19). Carpine and Sieber, 2021). Additionally, the World Health Organization (WHO) reported that human immunodeficiency virus (HIV) caused approximately 1 million deaths in 2017 (WHO, 2019). Moreover, the side effects of antiviral drugs and the increase in viral resistance have become critical medical concerns. Clinical studies on many cyanobacterial metabolites with antiviral properties have shown promising wide-range activity. Inhibiting the binding of viral proteins to host cells is the most common mechanism of cyanobacterial metabolites to prevent viral infection (Kar et al., 2022).

5.3.1 Cyanovirin-N (CV-N)

CV-N is a protein molecule having a unique sequence of 101-amino acid residues, purified from the genera *Nostoc ellipsosporum* (Xiong et al., 2010) and *Cyanothece* sp. (Matei t al., 2016). These protein molecules belong to the lectins class due to their ability to bind glycans (Demay et al., 2019). Yu et al. (2010) demonstrated that CV-N has a virucidal effect on Herpes simplex virus type-1 (HSV-1) in vivo and in vitro, which would make it a promising novel candidate for the development of anti-HSV drugs (Yu et al., 2010). Dey et al. (2000) have shown the antiviral effect of (CV-N) against human immunodeficiency virus type-1 (HIV-1) by binding with HIV envelope glycoprotein (gp 120) and blocking the bind of gp120 with cell-associated CD4 receptor (Dey et al., 2000). Cyanovirin-N also inhibits Human herpesvirus 6 (HHV-6), measles virus (Dey et al., 2000), Hepatitis C virus, influenza viruses, and Ebola (Carpine and Sieber, 2021).

5.3.2 Microvirin (MVN)

MVN is another cyanobacterial lectin, composed of 108 amino acids, also is more than 50-fold less cytotoxic than CV-N. Microvirin isolated from *Microcystis aeruginosa*, does not raise the level of activation markers including HLA-DR, CD25, and CD69 in CD4+T cells. Microvirin inhibits the formation of syncytium between HIV-1 infected T cells and uninfected CD4+ T cells (Sami et al., 2000).

5.3.3 Aplysiatoxins (ATXs)

ATXs are distinct polyketide classes of biologically active dermatoxins, purified from various cyanobacterial species, such as *Oscillatoria nigro-viridis*, *Lyngbya majuscula*, *Schizothrix calcicole*, and *Trichodesmium erythaeum* (Gupta et al., 2014). Aplysiatoxins have shown antiviral effects on Chikungunya's virus (CHIKV) by blocking the replication step of the CHIKV replicative cycle (Martins et al., 2020). ATXs have been shown to have potent tumor-promoting activity due to their ability to activate protein kinase C (PKC), this enzyme has a role in cellular proliferation, differentiation, and apoptosis (Nakagawa et al., 2009). In addition, two analogs of aplysiatoxin exhibit excellent bioactivity with potent blocking action against potassium channels (Han et al., 2018).

5.3.4 Scytovirin (SVN)

SVN is a single polypeptide chain with 95 amino acids and 9.7 kDa, purified from *Scytonema varium* (Moulaei et al., 2007). Scytovirin has potential activity against the human immunodeficiency virus (HIV) by binding with the envelope GP (gp160, gp120, and gp41) and inhibiting the virus in low nanomolar concentration. However, SVN does not bind to extracellular CD4 receptors or other types of cell surface protein. The ability of Scytovirin to inactivate the laboratory strains of (HIV-1) has made it a promising candidate for the development of anti-HIV therapeutics (McFeeters et al., 2007). Besides, Garrison et al. (2014) demonstrated the ability of Scytovirin to inhibit the replication of the Zaire Ebola virus (ZEBOV) by binding to the envelope glycoprotein. SVN inhibits the replication of the Zaire Ebola virus with an EC_{50} of 50 nM, and with a similar inhibitory concentration, SVN showed activity on the Angola strain of Marburg virus (MARV) (Garrison et al., 2014).

5.3.5 Ca-spirulan (Ca-Sp)

Ca-Sp is a sulfated polysaccharide, purified in 1996 from *Spirulina platensis* (Hayashi et al., 1996). Ca-spirulan prevents some viruses from replicating and shows potent effects against a series of enveloped viruses that include human cytomegalovirus (HVMV), herpes simplex virus, human immunodeficiency virus type-1, mumps virus, measles virus, and influenza virus (Tiwari and Tiwari, 2020). Whereas, Ca-spirulan seems inactive against non-enveloped viruses such as coxsackievirus and poliovirus (Hayashi et al., 1996). Some other sulfated polysaccharides like dextran sulfate or heparin have been known for their antiviral and anticoagulant activities. In comparison, Ca-spirulan presented low anticoagulants and long half-life in blood, which make it a promising potential to develop novel antiviral agents (Demay et al., 2019). Furthermore, ichthyopeptins A and B, are cyclic depsipeptides, purified from *Microcystis ichthyoblabe*, showed antiviral activity toward influenza A virus (Vijayakumar and Menakha, 2015). These studies indicated that cyanobacterial molecules are excellent sources of new antiviral agents.

6 The cyanotoxins (Microcystins) as promising potential pharmaceutical agents

Along with all these advantages, some freshwater cyanobacteria are well known to synthesize highly potent toxins called cyanotoxins. According to their toxicity, these cyanotoxins can be classified into hepatotoxins (nodularin and microcystin), dermatoxins (lyngbyatoxin-a), and neurotoxins (saxitoxins and anatoxin-a) (Sainis et al., 2010), that can pose a danger to human health and animals. Around 40 cyanobacterial species have been reported to have members that produce toxins such as *Oscillatoria*., *Lyngbya majuscula*., *Leptolyngbya*., *Anabaena*, *Nodularia*, *Microcystis*, and *Aphanizomenon* sp. (Dodds, 2002). Over the last few decades, microcystins (MCs) the most common and widespread among the cyanotoxins, have been evaluated for their potential biological activities. MCs are cyclic heptapeptidic toxins, extracted from cyanobacterium *Microcystis*, *Nostoc, Planktothrix*, and *Anabaena* contain a rich source of natural cytotoxic compounds with the potential to target cancerous cells through the expression of specific uptake (OATPs) transporters. Kounnis et al. (2015) revealed that the cyanobacterial cyclopeptide microcystin-LR showed anticancer activity on BxPC-3 and MIA PACA-2 pancreatic cancer cells by the expression of OATP1B1 and 1B3 the organic anion-transporting polypeptides. Thus,

microcystin-LR kills only cancer cells that express (AOTP) without affecting normal cells (Kounnis et al., 2015). In addition, microcystin-LR induces potent cytotoxic effects on Sp2/01 myeloma cancer cells. This molecule showed high inhibition activity with an IC_{50} value of 29-39 µl (Kailash et al., 2022). Microcystin has been suggested to be potent for anticancer drug development. Besides, Ramos et al. (2015) reported the antimicrobial activity of two microcystins (MC-LR and [D-Leu^1] MC-LR) and four extracts of *Microcystis aeruginosa* (methanol, chloroform, hexane, and aqueous) against *Mycobacterium tuberculosis* pan-susceptible (H37Rv), rifampicin- (RIFr) and isoniazid-resistant strains (INHr)., and nontuberculous mycobacteria*: Mycobacterium chelonae, Mycobacterium kansasii,* and *Mycobacterium terrae.* The four extracts of *Microcytis aeruginosa* were tested, and the results revealed that the hexane extract of *Microcystis aeruginosa* presented the highest antimycobacterial effects on *Mycobacterium tuberculosis* including both resistant and sensitive strains with MIC from 1.93 µM to 0.06 µM. Additionally, the MC-LR did not show antimycobacterial activity against the *M. tuberculosis* strains at the concentration of 53 µM, while [D-Leu1] MC-LR exhibited inhibitory activity with MIC 13.2 µM. Furthermore, both microcystins had high inhibitory activity against nontuberculous mycobacteria except *M. terrae* which was resistant to the microcystins with MIC of 1.08 µM and 6.74 µM for MC-LR and [D-Leu1] MC-LR, respectively. According to the results, [D-Leu1] MC-LR showed the highest antimycobacterial activity, which makes it a promising bioactive molecule to develop a novel antimycobacterial drug (Ramos et al., 2015). These studies revealed that microcystins are promising potential as anticancer and antimicrobial agents.

7 Current challenges and future prospective

While several cyanobacterial metabolites showed potential in all diseases treatment, only a few entered clinical trials Many challenges are related to the development of these drugs. The bioavailability and stability of cyanobacterial compounds, for example, peptides from cyanobacteria are unstable, for this these peptides require various stabilizing strategies such as replacing amino acids with other more resistant amino acids to structural restriction, stapling, hydrolysis, or cyclization. These strategies will be able to improve the bioavailability and stability of cyanobacterial peptides (Skowron et al, 2019). Another big concern is the limited knowledge of the synthesis of cyanobacterial compounds. The partially known regulations and function of the enzymes involved in biosynthetic processes and cellular pathways are complicated by using genetic engineering to increase the production of metabolites. Furthermore, the toxicity of some cyanobacterial compounds such as anatoxins, neurotoxins, microcystins, and saxitoxins raised serious concerns about deterring the use of cyanobacterial metabolites in the pharmaceutical and food industry, despite some of them have shown promising biological activities (Kar et al., 2022). To enhance drug production, genetic engineering techniques are undergoing development by converting the genetic data from the target molecule into the host cells (Mondal et al, 2020). Besides, antibody-drug conjugates (ADCs), given a single agent have shown anticancer efficiency in clinical trials research. Researchers are investing extensive efforts to develop next-generation ADCs by new targets identification and enhancing their pharmacological properties (Fuentes-Antrás et al., 2023).

8 Conclusion

In the last few decades, cyanobacteria have received attracted attention from biologists. The screening programs have demonstrated that cyanobacteria are a prominent source of novel molecules for pharmacology and medical therapeutics. Cyanobacteria are an immense source of many metabolites with various biological properties. The current review has shown the potential anticancer activity of cyanobacterial compounds against many types of cancer cells by inducing apoptosis. In addition, cyanobacteria inhibit various pathogenic microorganisms and have potential in the treatment of infectious diseases. These microorganisms have great potential to provide drugs for many different types of human diseases. Thus, cyanobacteria deserve an extensive investigation to find novel active substances from underexplored and extreme habitats which could be a source of future medicines.

Author Contributions

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Competing financial interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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