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Review Article

Therapeutics from Cyanobacteria: A Review of Cyanobacteria-Derived Compounds as Anti-cancer Drug Leads

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ABSTRACT

Cancer is a group of illness that collectively are the second highest cause of death globally after cardiac disease. They can also affect the social, psychological, physical and economic well-being of individuals, families and societies. Novel drug discovery for new cancer chemotherapeutics is a lengthy, complex, and costly process. Cancer drugs that are currently in clinical use have several drawbacks, including serious undesirable side-effects and the development of resistance to anticancer drugs. Thus, the development of novel effective and low toxicity cancer drugs is a priority for medical science. In recent decades, natural products-derived cancer drug discovery has become a promising avenue for drug development and an increasing number of studies have been published. Cyanobacteria have potential as a source for novel drug discovery. Cyanobacterial bioactive metabolites have a large diversity of chemical structures, modes of action and therapeutic targets. Multiple cyanobacteria-derived compounds have successfully reached clinical trials, and some have already been approved by regulatory authorities including the FDA as anticancer drugs. This review highlights the therapeutic potential of cyanobacteria in cancer drug discovery and summarizes the cyanobacterial compounds already used as cancer chemotherapies. The review aims to highlight cyanobacteria as sources of potential new drugs and focus future research on this field.

Keywords: Cyanobacteria, Bioactive compounds, Drug discovery, Anti-cancer compounds, Apoptosis, Clinical trials.

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INTRODUCTION

Cancer is one of the most widespread and highest mortality diseases worldwide.[1,2] Approximately 18 million new cases of cancer were recorded globally in 2018, resulting in approximately 10 million deaths.[1,2] The prevalence of cancer has been increasing significantly over the past decades due to risks associated with increased age, environmental factors and changes in lifestyle.[1,2] Non-Melanoma Skin Cancer (NMSC) is the most reported cancer in North America, Australia and New Zealand, each of which have amongst the highest incidence rates globally.[3] As well as being amongst the most diagnosed types of cancer, lung and breast cancer are major causes for cancer-related death in both males and females.[4] The causes of cancer are numerous and vary widely. Cancers may develop due to both external (e.g., tobacco, chemicals, radiation, and infectious organisms) and internal factors (e.g., genetic weaknesses, immune conditions).[1-3]

Chemotherapy is one of the most frequently practiced and most effective treatments for many types of cancer as it halts the growth and proliferation of cancer cells, and may also preferentially kill them.[5] Chemotherapeutic agents vary on the basis of their therapeutic efficacy and side effects. Certain chemotherapeutics have potent cytotoxic effects, yet many also have serious side effects including nausea, vomiting, hair loss, fatigue, hearing impairment, decreased immune function and susceptibility to infection, low blood platelet levels, decreased red and white blood cells count, loss of appetite and bowel problems.[6-8] Moreover, chemotherapeutic agents are generally expensive due to limited supply. The process of cancer drug development is costly and time consuming. Notably, some tumour cells develop resistance against cancer chemotherapeutics, including the vinca alkaloids and taxanes, which is a major reason for the failure of chemotherapeutic treatments against some cancers.[9,10] Furthermore, new varieties of cancer, such as gliobastoma are continually arising and increasing in prevalence, making cancer one of the leading causes for human death and one of the most

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Table 1: Cyanobacterial metabolites with anticancer activity.

Compound name	Chemical class	Organism	Anti-cancer Spectrum	References
Ankaraholide A	Glycosylated swinholide	*Geitlerinema* sp.	MDA-MB-435 Breast cancer NCI-H460 lung cancer.	[32]
Apratoxin A	Cyclic depsipeptide	*Lyngbya majuscula*	HT29 colon adenocarcinoma HeLa cervical carcinoma U2OS osteosarcoma.	[33,34]
Apratoxin A sulfoxide	Cyclic depsipeptide	*Moorea producens*	NCI-H460 lung cancer.	[35]
Apratoxins B	Cyclic depsipeptide	*Lyngbya* sp.	LoVo colon cancer KB oral epidermoid cancer.	[36,37]
Apratoxins C	Cyclic depsipeptide	*Lyngbya* sp.	LoVo colon cancer KB oral epidermoid cancer.	[36,37]
Apratoxins D	Cyclic depsipeptide	*L. sordida*	H-460 lung cancer.	[38]
Apratoxin E	Cyclic depsipeptide	*L. bouilloni*	H-460 lung cancer U2OS osteosarcoma HeLa epithelial carcinoma HT29 colonadenocarcinoma.	[34]
Apratoxins F and G	Cyclic depsipeptide	*L. bouilloni*	HCT-116 colorectal cancer cells.	[39]
Apratoxin H	Cyclic depsipeptide	*M. producens*	NCI-H460 lung cancer.	[35]
E-dehydroapratoxin A	Cyclic depsipeptide	*L. bouillonii*	U2OS oscteocarcoma HT-29 colon carcinoma HeLa cervical carcinoma.	[34]
Aeruginoguanidines 98-A, 98-B, and 98-C	Cyclic peptide	*M. aeruginosa*	P388 (leukemia) cells.	[40]
Aurilide B and C	Cyclic depsipeptide	*L. majuscula*	NCI-H460 lung tumor neuro-2a mouse neuroblastoma.	[41]
Belamide A	Tetrapeptide	*Symploca* sp.	HCT-116 colon cancer.	[42]
Benzylthio ether 45	Phenyl ether	*L. majuscula*	HCT-116 colon cancer.	[43]
Biselyngbyaside	Glicomacrolide	*Lyngbya* sp.	HeLa S3 cervical cancer HL60 leukemia Normal rat kidney cells extracellular signal-regulated protein kinase.	[44]
Biselyngbyaside A, B	Glicomacrolide	*Lyngbya* sp.	HeLa S3 cervical cancer HL60 leukemia.	[44,45]
C-Phycocyanin	Pigment-protein complex	*Spirulina platensis*	MDA-MB-231 breast cancer.	[46]
Carmaphycin A, B	β-epoxyketone	*Symploca* sp.	H-460 lung adenocarcinoma HCT-116 colon cancer.	[47]
Calothrixin A	Pentacyc licindolo phenanthridine	*Calothrix* sp.	HeLa epithelial carcinoma, Human leukemia CEM cells, Jurkat.	[48-51]
Calothrixin B	Pentacyc licindolo phenanthridine	*Calothrix* sp.	HeLa epithelial carcinoma, Leukemia CEM	[48,50,52]
Caylobolide A	Macrolactone	*L. majuscula*	HCT-116 colon tumor.	[53]
Caylobolide B	Macrolactone	*Phormidium* sp.	HeLa cervical carcinoma and HT29 colorectal adenocarcinoma.	[54]
Cocosamides A and B	Cyclic depsipeptide	*L. majuscula*	MCF7 breast cancer HT29 colon cancer.	[55]

Compound name	Chemical class	Organism	Anti-cancer Spectrum	References
Coibacin A-D	Polyketide	*Oscillatoria* sp.	NCI-H460 lung cancer.	[56]
Coibamide A	Cyclic depsipeptide	*Leptolyngbya* sp.	NCI-H460 lung cancer MDA-MB-231 breast cancer LOX IMVI melanoma HL-60 myeloid cells SNB75 astrocytoma U87-MG and SF-295 glioblastoma cells.	[57,58]
Cryptophycin-1	Cyclic depsipeptide	*Nostoc* sp.	Several human cancer cell lines, including SKOV3 ovarian carcinoma and Human MDA-MB-435 mammary adenocarcinoma cells.	[59]
Curacin A	Lipopeptide	*L. majuscula*	A549 lung cancer MCF-7 breast cancer.	[25,60]
Dolastatin 10	Linear pentapeptide	*Symploca* sp.	Human lung cancer cells.	[60]
Dragonamide	Lipopeptide	*L. majuscula*	HT-29 colon adenocarcinoma, A-549 lung epithelial adenocarcinoma, and MEL-28 melanoma.	[61]
Hectochlorin	Lipopeptide	*Lyngbya majuscula*	Jurkat CEM leukemia Molt4 T cell leukemia A549 lung cancer U266 myeloma M21 melanoma.	[62]
Hierridin A-C	Cyclic peptide	*Cyanobium* sp.	HT-29 colon adenocarcinoma.	[63]
Hoiamide A	Cyclic depsipeptide	*Phormidium gracile* and *L. majuscule*	H-460 lung cancer.	[64]
Homodolastatin 16	Cyclic depsipeptide	*L. majuscula*	ME180 cervical cancer, WHCO1, and WHCO6 esophageal cancer.	[65]
Hormothamnin A	Cyclic undecapeptide	*Hormothamnion enteromorphoides*	HCT-116 colorectal carcinoma SW1271 lung cancer A549 lung cancer B16-F10 melanoma.	[66]
Kohamamides A, B, and C	Cyclic depsipeptide	*Okeania* sp.	HL60 cells human leukemia.	[67]
Lagunamide A and B	Cyclic depsipeptide	*L. majuscula*	P388 murine leukemia cells.	[68]
Lagunamide C	Cyclic depsipeptide	*L. majuscula*	Cancer prostate PC3, ovary cancer SK-OV, lung adenocarcinoma A549 and ileocecal colorectal cancer HCT8 cells.	[69]
Largazole	cyclic depsipeptide	*Symploca* sp.	U2OS osteosarcoma and MDA-MB-23I breast cancer.	[70]
Laxaphycin	Cyclic peptide	*Anabaena laxa*	HCT-116 colon cancer.	[71]
Lyngbouilloside	Glycosidic macrolide	*L. bouillonii*	Neuro-2a Neuroblastoma.	[72]
Lyngbyabellin A	Cyclic depsipeptide	*L. majuscula*	LoVo colon adenocarcinoma and KB nasopharyngeal carcinoma.	[62]
Lyngbyabellin B	Cyclic depsipeptide	*L. bouillonii*	HT-29 Colon carcinoma HeLa Cervical carcinoma.	[73]

Compound name	Chemical class	Organism	Anti-cancer Spectrum	References
Lyngbyabellin J	Cyclic depsipeptide	*L. bouillonii*	HT-29 Colon carcinoma HeLa Cervical carcinoma.	[73]
Lyngbyabellin N	Cyclic depsipeptide	*L. bouillonii*	H-460 Lung cancer HCT-116 Colorectal carcinoma.	[74]
Lyngbyaloside B	Glicomacrolide	*Lyngbya* sp.	LoVo colon adenocarcinoma and KB nasopharyngeal carcinoma.	[75]
2-Epi-lyngbyaloside	Halogenated macrolides	*L. bouillonii*	HT-29 Colon carcinoma HeLa Cervical carcinoma.	[73]
18E-lyngbyaloside C	Macrolide	*L. bouillonii*	HT-29 Colon carcinoma HeLa Cervical carcinoma.	[73]
18Z-lyngbyaloside C	Macrolide	*L. bouillonii*	HeLa Cervical carcinoma.	[73]
27-Deoxylyngbyabellin A	Macrolide	*L. bouillonii*	HT-29 Colon carcinoma HeLa Cervical carcinoma.	[73]
Majusculamide C	Cyclic depsipeptide	*L. majuscula*	Glioblastoma SF-295, colorectal cancer KM20L2, ovarian carcinoma OVCAR-3, kidney cancer A498 and lung cancer NCI-H460 cells.	[76]
Malevamide D	Peptide ester	*S. hydnoides*	HT-29 colon cancer P-388 lymphoma A-549 lung cancer MEL-28 melanoma.	[77]
Malyngamide 2	Lipopeptide	*L. sordida*	H-460 lung cancer.	[78]
Malyngamide 3	Lipopeptide	*L. majuscula*	MCF7 breast cancer HT29 colon cancer.	[55]
Malyngamide 4, A and B	Lipopeptide	*L. majuscula*	MDA-MB-231 breast cancer HT-29 colon cancer A-549 lung cancer.	[79]
Malyngamide C	Lipopeptide	*L. majuscula*	HT-29 colon cancer H-460 lung cancer NCI-H460 lung cancer Neuro-2a Neuroblastoma HCT-116 colon cancer.	[79-81]
Malyngamide J and K	Cyclic depsipedtide	*L. majuscula*	NCI-H460 lung cancer Neuro-2a Neuroblastoma.	[81]
6-O-acetylmalyngamide F	Cyclic depsipedtide	*L. majuscula*	NCI-H460 lung cancer Neuro-2a neuroblastoma.	[79]
8-O-acetyl-8-epi-malyngamide	Cyclic depsipedtide	*L. majuscula*	NCI-H460 lung cancer.	[79]
8-Epi-malyngamide C	Cyclic depsipedtide	*L. majuscula*	NCI-H460 lung cancer Neuro-2a neuroblastoma.	[79]
Microcyclamide	Cyclic hexapeptide	*M. aeruginosa*	P388 murine leukemia cells.	[82]
Molassamide	Depsipeptide	*Dichothrix utahensis*	MCF-7 breast cancer.	[83]

Compound name	Chemical class	Organism	Anti-cancer Spectrum	References
Nostocyclopeptide A1 and A2	Cyclic heptapeptides	*Nostoc* sp.	LoVo colon cancer and KB oral epidermoid cancer.	[84]
Obyanamide	Cyclic depsipedtide	*L. confervoides*	LoVo colon cancer and KB oral epidermoid cancer.	[85]
Palauamide	Cyclic depsipeptide	*Lyngbya* sp.	Gastrocarcinoma BGC, cervical carcinoma HeLa, lung adenocarcinoma A549 cells and KB oral epidermoid cancer.	[86,87]
Palmyramide A	Cyclic depsipeptide	*L. majuscula*	H-460 lung cancer.	[88]
Pitipeptolide A-F	Cyclic depsipeptide	*L. majuscula*	MCF-7 breast cancer HT29 colon cancer LoVo colon cancer.	[89, 90]
Pitiprolamide	Cyclic depsipeptide	*L. majuscula*	MCF7 breast adenocarcinoma and HCT116 colorectal carcinoma cells.	[91]
Pseudodysidenin	Lipopeptide	*L. majuscula*	HT-29 colon Adenocarcinoma, MEL-28 melanoma, and A-549 lung adenocarcinoma cells.	[92]
Somocystinamide A	Lipopeptide	*L. majuscula*	Jurkat CEM leukemia Molt4 T cell leukemia A549 lung cancer U266 myeloma M21 melanoma NB7 Neuroblastoma MCF-7 breast cancer PC3 prostate cancer.	[93]
Symplocamide A	Cyclic peptide	*Symploca* sp.	H-460 lung cancer Neuro-2a neuroblastoma.	[94]
Symplostatin 1	Linear pentapeptide	*S. hydnoides*	NCI/ADR ovarian cancer SRB MDA-MB-435 breast cancer SKOV-3 ovarian cancer.	[95,96]
Scytophycin A-E	Cyclic c depsipeptides	*Scytonema pseudohofmanni*	KB nasopharyngeal carcinoma.	[97]
Tasiamide	Cyclic peptide	*Symploca* sp.	LoVo colon cancer KB oral epidermoid cancer cells.	[98]
Tasipeptins A and B	Cyclic depsipeptides	*Symploca* sp.	KB oral epidermoid cancer cells.	[99]
Thiol 46 (S)-7-methoxytetradex-4(E)-enoic acid	Lipopeptide	*L. majuscula*	MDA-MB-231 breast cancer.	[79]
Tiglicamide	Cyclic depsipeptides	*L. confervoides*	Epidermal growth factor receptor (EGFR) lung cancer.	[100]
Ulongapeptin	Cyclic depsipeptide	*Lyngbya* sp.	KB oral epidermoid cancer cells.	[101]
Viqueamide A	Cyclic depsipeptide	*Rivularia* sp.	H-460 lung cancer.	[102,103]
Veraguamides A-G	Cyclic depsipeptides	*S. cf. hydnoides*	HT-29 colon cancer HeLa cervical cancer.	[104,105]
Wewakazole	Cyclic depsipeptide	*L. sordida*	H-460 lung cancer.	[78]
Wewakpeptins	Depsipeptides	*L. semiplena*	H-460 lung cancer.	[106]

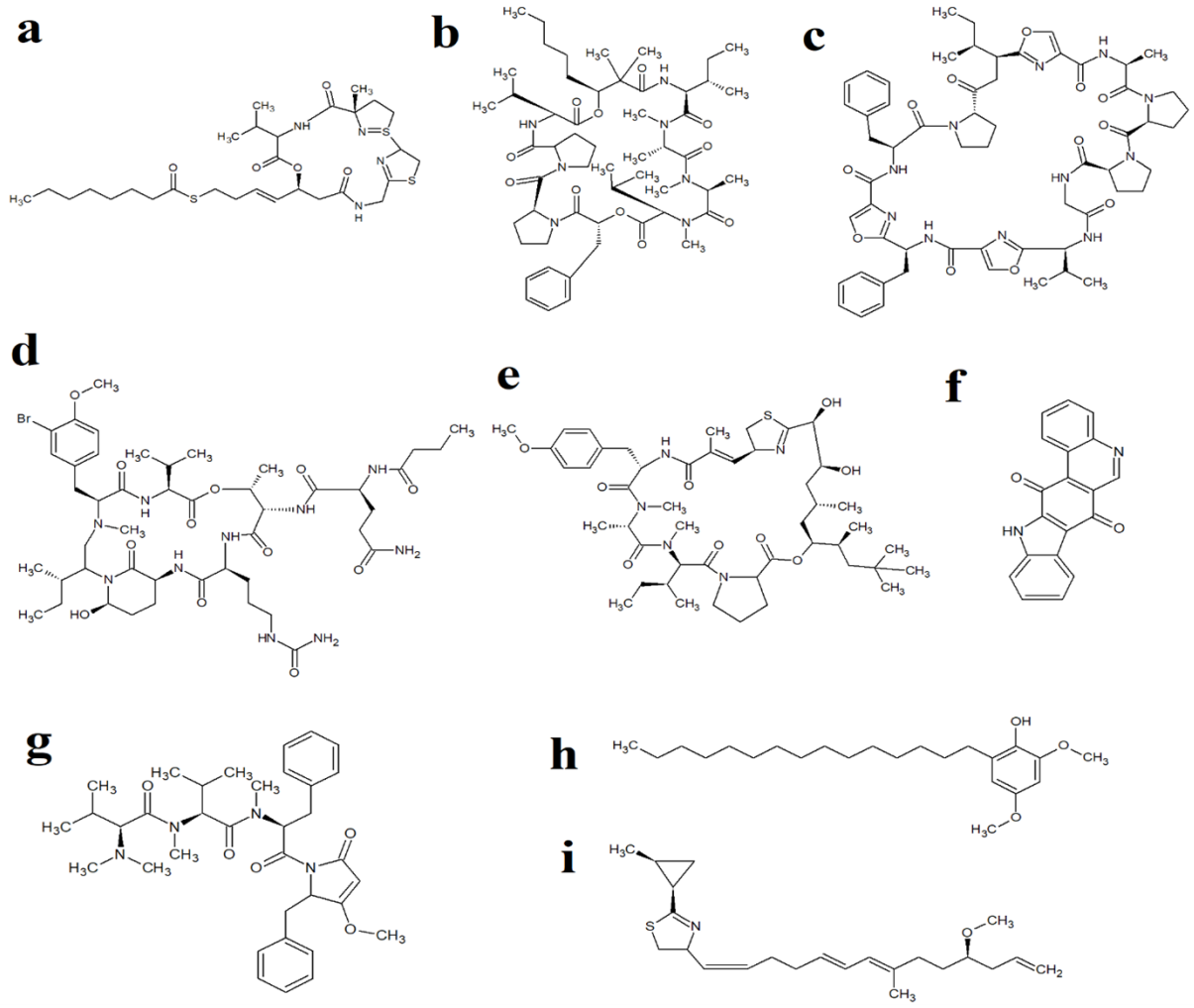

Figure 1: Chemical structures of selected cyanobacterial secondary metabolites with anticancer potential: (a) largazole, (b) wewakpeptin D, (c) wewakazole, (d) symplocamide A, (e) apratoxin D, (f) calothrixin B, (g) hierridin B, (h) (+)-curacin A, and (i) belamide A.

difficult diseases to treat effectively.[11] It is vital to screen for suitable therapeutic agents with low or no side effects, as well as enhanced efficacy against cancer cells to maintain a dynamic pipeline for new anticancer drug leads.

Screening natural sources for novel pharmacologically active compounds is promising. Molecules derived from natural sources are commercially available in the market as anti-tumour and anti-infective drugs (e.g. penicillin, amphotericin B, taxol and cyclosporin).[12-17] Indeed, over 60% of approved anticancer drugs and drug candidates reaching clinical usage between 1981 and 2020 were natural compounds, or molecules derived from natural compounds by semi-synthesis.[18-20] Recently, the exploration of active compounds from natural sources has received substantial attention due to the positive effects of these compounds on health.[21-23] Several compounds derived from natural sources are currently undergoing preclinical and clinical trials as potent anticancer drugs.[24] Early studies screening cyanobacteria for novel anticancer compounds began in the laboratories of Moore (Oregon State University) and Gerwick (University of Hawaii) in the 1990s.[25] Since then, cyanobacteria have become a promising (yet still relatively unexplored) natural resource of potential anticancer agents.

Cyanobacteria metabolites as cancer drug leads

Cyanobacteria are a natural resource that are rich with biologically active compounds.[26] The metabolites can be extracted from the biomass (intracellular) or from cultured media (extracellularly released metabolites) as therapeutically effective compounds.[27,28] The production of active secondary metabolites in cyanobacteria is reliant on their complex genetic makeup. They have relatively large (over 60 kb) biosynthetic gene clusters.[29] These clusters use three unique biosynthetic pathways or hybrids thereof: non-ribosomal peptide synthetases (NRPS), polyketide synthases (PKS), and ribosomal synthesis (RS).[29] Notably, cyanobacteria have the ability to rapidly switch between these pathways depending on the environmental and growth conditions that they are exposed to.[30] These factors allow cyanobacteria to synthesize hundreds of structural variants with significant biological properties. The secondary metabolites that

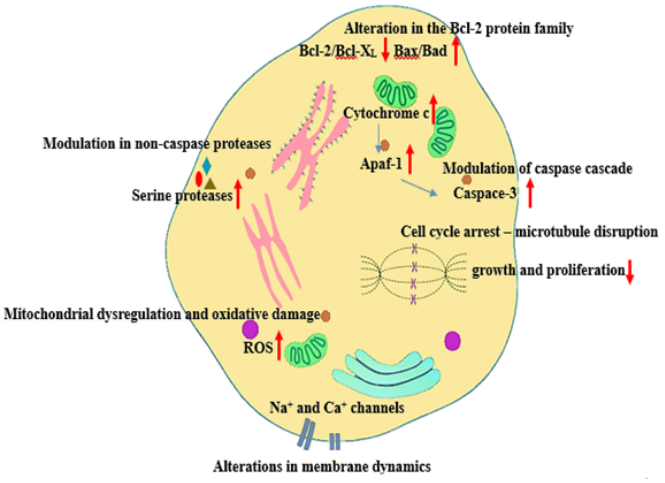

Figure 2: Pathways used by cyanobacterial metabolites to induce apoptosis in cancer cells.

exert anticancer potential are from diverse chemical classes, including peptides (linear peptides, cyclic peptides, lipopeptides, depsipeptides, and cyclic depsipeptides), swinholides, fatty acid amides, macrolactones, glicomacrolides, polyketides, alkaloids, terpenoids and lipids.[31] Another benefit of cyanobacteria as a microbial source for drug discovery lies in the economy of their cultivation compared with other microorganisms, as they require only simple inorganic nutrients for growth. Thus, cyanobacteria have the potential for expanded utilization in drug discovery for cancer chemotherapeutics. This review focuses on promising natural compounds from cyanobacteria that have potential for the development of anti-cancer therapeutics. Table 1 summarizes some promising anticancer metabolites originated from cyanobacteria, whilst the structures of selected compounds are shown in Figure 1. These metabolites are known to induce apoptosis in cancer cells by multiple molecular mechanisms.

Anticancer mechanisms of cyanobacterial metabolites

Cyanobacteria are an emerging source for novel cancer drug discovery. Cyanobacterial metabolites with anticancer activity may inhibit the growth, survival and proliferation of cancer cells via multiple pathways, including cell-cycle arrest, regulation of caspase cascades, modulation of non-caspase proteases, mitochondrial dysregulation, induction of oxidative stress, regulation of Bcl-2 proteins and alterations in membrane dynamics (particularly in sodium and calcium channels).[107-111] Figure 2 provides an overview of known anticancer pathways of cyanobacteria-derived metabolites.

Cell-cycle arrest

Cell cycle arrest is an important regulatory mechanism that inhibits the growth of cells by blocking their division. Some anticancer compounds derived from cyanobacteria can effectively block the cell-cycle by interfering with normal cellular functions that require tubulin and actin protein polymerisation. Microtubule and actin filaments are vital in the movement of chromosomes and cytoskeleton components during cell division. Disruption of tubulin and actin proteins may therefore block cell division, ultimately leading to the cell-cycle arrest.[111] A synthetic analog of the cyanobacterial-derived compound cryptophycin (cryptophycin 52), a macrocyclic depsipeptide derived from *Nostoc* sp., and calothrixin A, a pentacyclic alkaloid isolated from *Calothrix* sp., induce cell cycle arrest during the G2/M phase of the cell cycle by disrupting tubulin and actin polymerization in multiple types of human cancer cells (leukemia CEM cells, Jurkat, prostate cancer cells, LNCaP, PC-3 and DU-145).[112,113] The cytotoxic tetrapeptide compounds dolastatin 10 and dolastatin 15, isolated from *Symploca* sp., also induce cell cycle arrest in several cancer cells in G2/M phase.[100,114] Notably, *dolastatin* 10 (also known as symplostatin 1) has recently been approved by the food and drug administration (FDA) for use as a cancer chemotherapeutic.[115] In addition to inducing cell cycle arrest, calothrixin A, interferes with DNA replication during the S phase of cell cycle in CEM leukemia cells at concentrations ranging from 1 μM to 10 μM.[112] Lyngbyabellin B (a cytotoxic cyclic depsipeptide) and hectochlorin (a cytotoxic lipopeptide), which are both isolated from cyanobacteria of the genus *Lyngbya*, exhibit strong anti-proliferative effects by blocking cell cycle progression in the G2/M phase in a human Burkitt lymphoma cell line by disrupting the cellular microfilament network.[106,110] Similarly, the therapeutic potential of apratoxin A (a cytotoxic cyclic depsipeptide isolated from several cyanobacterial species of the genus *Lyngbya*), demonstrates anti-proliferative activity against HeLa cervical carcinoma.[33] Apratoxin A is a potent inhibitor of the cell cycle in G1 phase at a dose of 50 nM.[33] Similarly, calothrixin B, induces G1 arrest at 0.1 μM in CEM leukemia cells.[50] Additionally, coibamide A, a potent cytotoxic depsipeptide isolated from the cyanobacterium *Leptolyngbya* sp., induces cell cycle arrest in the G1/S phase transition in U87-MG and SF-295 glioblastoma cells.[58]

Modulation of caspase apoptosis cascade

Caspases are a group of cysteine proteases that induce apoptosis (active/programmed cell death).[116] Caspase driven apoptosis is achieved through a number of cascading processes, which include the cleavage of proteins in the cell, followed by cell disassembly, cell death, and ultimately phagocytosis and removal of the cell debris.[116] Specific metabolites from cyanobacteria can modulate these caspase cascades, ultimately inducing cell death/apoptosis.[116] Extracts from some *Anabaena* species have anticancer activity against acute myeloid meukemia (AML) cells by modulating the caspase response, leading to apoptosis.[117,118] Those studies reported a substantially higher number of cells undergoing apoptosis following exposure to the *Anabaena* sp. extracts compared to the control.[118] This is a particularly interesting finding as AML cells are prone to develop resistance

to cancer chemotherapeutics, making the discovery of effective drugs against AML a priority.

Caspase-3 has received a great deal of interest as a target for cancer therapy as it is considered to be a key effector protein in the induction of apoptosis.[96] One study reported that activation of caspase-3 initiated apoptosis in MDA-MB-435 cells exposed to symplostatin 1 isolated from cyanobacteria of the genus *Symploca*.[96] Another study reported an increase in caspase-3 activity in a similar manner to the apoptosis inducer cycloheximide. Additionally, cryptophycin 1 induces substantial activation of the caspase-3 cascade in SKOV3 human ovarian carcinoma cells, thereby initiating apoptosis.[63] Similarly, dolastatins 10, 15 and curacin A also stimulate caspase-3 induced apoptosis in A549 lung cancer cells.[60] Apoptosis was also induced in the human prostate cancer cell lines LNCaP, PC-3 and DU-145 following, exposure to cryptophycin 52, and the activity was shown to be induced by both caspase-3 and caspase-1 activation.[107] The lipopeptide somocystinamide A (isolated from *L. majuscula*), activates caspase-8 to initiate alterations in the cell membrane and apoptotic cell death in Jukrat and CEM leukemia cells, as well as A549 human lung cancer, MCF-7 breast cancer and PC3 prostate cancer cell models.[93]

Modulation of non-caspase proteases

Despite the crucial role played by caspases in apoptotic cell death, apoptosis often continues following the suppression of these proteins.[120,121] Other non-caspase protease initiators may also contribute to apoptosis when caspases are suppressed. It has been suggested that these non-caspase proteases to have caspase-like functions in the induction of cell death.[64,125] Proteases are proteolytic enzymes that have multiple vital cellular functions in DNA replication, cell cycle progression, proliferation, as well as in apoptosis.[122] The ability of some serine proteases to induce apoptosis-like cell death via intracellular proteolysis has previously been described and is the focus of ongoing research.[124]

Cyanobacterial-derived anticancer compounds also target functions mediated by the serine proteases, including the pancreatic enzymes elastase, chymotrypsin and trypsin.[94] Kempopeptin A, a cyclodepsipeptide isolated from *Lyngbya* sp., inhibits the non-caspase serine protease, α-chymotrypsin at an inhibition concentration (IC_{50}) of 2.6 μM and elastase at 0.32 μM. Similarly, kempopeptin B has an IC_{50} against trypsin of 8.4 μM.[124] Another study observed selective inhibition of porcine pancreatic elastate by lyngbyastatin at IC_{50} values ranging from 3 to 10 nM.[125] *Microcystis* sp. are considered to be a good source of serine protease inhibitors including micropeptins, cyanopeptolins, microviridins, microginins and aeruginosins.[126] These compounds exhibit strong inhibitory activity against one or more serine proteases (including trypsin, plasmin, thrombin, elastase and chymotrypsin) in laboratory studies.[127-129] Interestingly, two novel compounds isolated from *Microcystis* sp. were good inhibitors of serine proteases. Micropeptin TR1058 inhibits chymotrypsin, with an IC_{50} of 6.78 μM.[130] The same study showed that aeruginosin TR642 inhibits trypsin and thrombin, with IC_{50} values of 3.80 and 0.85 μM, respectively.[130]

Mitochondrial dysregulation and oxidative damage

Mitochondria have a vital role in cellular function by producing energy for the majority of aerobic metabolic processes.[132] Interference in the normal functioning of the mitochondria imbalances vital cellular biochemical reactions, ultimately leading to apoptosis.[131] Mitochondria are important for the survival of all cells, including cancer cells. Moreover, mitochondria control the production and of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) and therefore can regulate both cellular proliferation and cell survival.[131] The ability of some cyanobacterial-metabolites in deregulating mitochondrial functions is well established. One study demonstrated the activation of the proteolytic processing of optic atrophy 1 (OPA1) in mitochondria as a result of the interaction of aurilide A and B (isolated from a marine cyanobacteria), with the Protein prohibitin 1 (PHB1), ultimately leading to apoptosis in HeLa cells via disruption of the mitochondria.[132]

Oxidative stress induces overproduction of ROS, leading to mitochondrial damage.[133] The natural balance between ROS and antioxidants in the cellular environment is compromised during oxidative stress by the overproduction of free radicals.[134] These free radicals subsequently induce DNA damage, degradation of proteins and lipids, as well as protein deposition.[134] DNA fragmentation is the most widely observed consequence of oxidative damage, which occurs after exposure to anticancer compounds derived from cyanobacteria. Calothrixin A (isolated from the cyanobacterium of the *Calothrix* genus) induces DNA fragmentation in human Jurkat cancer cells by inducing intracellular generation of ROS, resulting in apoptotic cell death.[48,51] Similarly, the cyanobacteria derived anticancer agents, dolastatin 10, as well as cryptophycins 1 and 52, also cause cell death in multiple human cancer cells by inducing intracellular DNA fragmentation.[59,60] Cyanobacterial metabolite-induced oxidative stress can also lead to the formation of binucleated cells. These metabolites include swinholide A, lyngbyabellin and symplostatin 1, which induce apoptosis in several cancer cells by breaking down the nucleus and forming binucleated and/or multinucleated cells[32,96,135]

The human body uses multiple antioxidants to overcome the harmful effects of free radicals and oxidative damage. These antioxidants can be either exogenous or endogenous (superoxide dismutase, glutathione, catalase, peroxidases, lipoic acid, l-arginine and coenzyme Q10). Sourcing exogenous antioxidants from natural sources has received substantial recent interest.[136] Cyanobacteria genera including *Spirulina, Microcystis, Synechococcus, Trichodesmium, Cyanothece,*

Oscillatoria, Anabaena and *Prochlorothrix* produce compounds with substantial antioxidant properties, including c-phycocyanin, carotenoids and phycobiliprotein.[137-139]

Alteration in the Bcl-2 protein family

The Bcl-2 protein family is located on the outer membrane of mitochondria and is divided into pro-apoptotic (Bad, Bax and Bak) and anti-apoptotic (Bcl-2 and Bcl-XL) proteins. Bcl-2 proteins regulate apoptosis by altering permeability of the outer mitochondrial membrane.[140] Anti-apoptotic proteins inhibit the release of mitochondrial cytochromes, thereby preventing apoptosis.[141] In contrast, Bax and Bak allow cytochrome c to pass through the mitochondrial membrane, thereby inducing apoptosis. Several cyanobacteria metabolites strongly inhibit Bcl-2 and Bcl-XL function in cancer cells.[96,107,142] Cyanobacterial-metabolites promote phosphorylation, subsequently downregulating the anti-apoptotic proteins. Symplostatin 1 inhibits Bcl-2 and reduces the total proteins via phosphorylation in breast cancer cell lines[96] A study using leukemia cell lines reported phosphorylation of the Bcl-2 proteins by dolastatin 10.[142,143] Similarly, cryptophycin 52 induced the phosphorylation of Bcl-XL and Bcl-2, in cancer cell lines, leading to cell death.[107] Another study reported that dolastatins 10 and 15 and curacin induce apoptosis via dephosphorylation of Bad serine-136 protein in A549 cells.[60]

Alterations in membrane dynamics (particularly in sodium and calcium channels)

Modulation of sodium and calcium channels has been reported for several cyanobacterial compounds.[64,144,145] Calcium and sodium ion channels, (together with other ion channels) help maintain "electro-ionic" balance on the surface of the cells.[146] These voltage gated ion channels are key regulators of rapid bio-electric signaling by maintaining homeostatic levels of sodium and potassium ions across cell membranes.[146] Early increases in sodium ion concentration, as well as dysfunctional volume regulation, are generally associated with the onset of apoptosis.[147-149] Hermitamides A and B block sodium ion channels by approximately 50% at 1 μM and 80% at 1 μM in HEK 293 human embryonic kidney cells, respectively.[143] Although the mechanism remains to be thoroughly examined, antillatoxin (another potent anticancer agent isolated from the cyanobacterium species, *L. majuscula*) rapidly increases intracellular sodium ion concentration in primary rat cerebellar granule cells.[145] Furthermore, in primary cultures of neocortical neurons from embryonic mice, hoiamides A and B induce sodium ion channels on the cell surface at an IC_{50} of 1.7 μM and 3.9 μM respectively, ultimately inducing cell death.[64]

It has been suggested that calcium ion entry into the cell is key to apoptosis induction.[150] Targeting calcium-entry channels or exchangers may promote apoptosis in some cancer cells.[150] Although, the evidence for calcium ion-related anti-cancer mechanisms driven by cyanobacteria metabolite is scarce, alotamide A (isolated from *L. bouillonii*), has been reported to increase calcium influx into murine cerebrocortical neurons at an EC_{50} of 4.18 μM and is considered a potential drug lead for cancer therapy.[151]

Cyanobacteria-derived compounds in clinical trials against cancers

Cyanobacteria are an emerging source of biologically active metabolites with a wide array of structural diversity. Cyanobacterial metabolites are often unique, and some have significant medicinal properties against human diseases.[152] Indeed, some of these metabolites have reached phase II and Phase III clinical trials as anticancer drugs.[100] Cryptophycins, dolastatins, and their derivatives, as well as several semi-synthetic analogs based on these molecular scaffolds, are currently undergoing clinical trials under the name as brentuximab vedotin (under the trademark Adcetris®).[153,154] Dolastatin 10 received approval by the FDA in 2011 against Hodgkin's lymphoma.[115] Table 2 summarises cyanobacteria-derived cancer drugs currently in clinical trials.

Although the hope for development of drugs from cyanobacteria is promising, there are several hurdles to the development of cyanobacterial cancer chemotherapies. Cyanobacterial-derived compounds may also have substantial negative side effects on patients, including fatigue, nausea, diarrhea, vomiting, alopecia, constipation, skin rash, decreased appetite and decrease in hemoglobin.[155-158] However, no life-threatening side effects have been reported from the cyanobacterial-derived cancer drugs currently under clinical trials and/or already in use.

ASG-15ME is a novel antibody-drug conjugate (ADC), which is linked to monomethyl auristatin E (MMAE), a derivative of the naturally occurring cyanobacterial cytotoxic compound, auristatin, and is currently in phase I clinical trials as an anticancer drug.[178] ASG-15ME has high affinity to SLITRK6, a member of neuronal transmembrane protein family. SLITRK6 is highly expressed in multiple tumors, including lung, skin, breast, glioblastoma and some bladder cancers, although there is low or moderate expression in normal human cells. ASG-15ME induces cell cycle arrest during mitosis by releasing microtubule-disrupting agent (MMAE), selectively targeting cancer cells that have higher expression of SLITRK6.[155] In a clinical study published in 2016, forty-three urothelial cancer patients were administered ASG-15ME at 0.1 to 1.25 milligrams per kilogram (mg/kg) weekly for three weeks on and one week off cycles. Interestingly, twenty-seven patients (63%) were able to achieve either complete remission, partial remission or a stable disease state. However, 43% and 20% of the patients reported fatigue and nausea, respectively. Furthermore, peripheral neuropathy was observed in 30% of the patients. Reversible corneal abnormalities also developed in eight patients. Despite

Table 2: Cyanobacteria-derived cancer drugs in clinical trials.

Brand Name	Cyanobacteria	Natural product or derivative	Company	Trial status	Cancer spectrum	References
ASG-15ME	*Caldora penicillata*	Derivative	Agensys and Seattle Genetics	Phase I	Metastatic urothelial cancer.	[155]
Brentuximab vedotin	*S. hydnoides* and *L. majuscula*	Derivative	Seattle Genetics	Approved by FDA and EMA	Hodgkin's lymphoma.	[156]
Denintuzumab mafodotin	*C. penicillata*	Derivative	Seattle Genetics	Phase II	Diffuse large B-cell lymphoma.	[157-159]
Depatuxizumab Mafodotin	*C. penicillata*	Derivative	Abbott laboratories and AbbVie	Phase III	diffuse intrinsic pontine glioma.	[117]
Enfortumab vedotinejfv (PADCEV™)	*C. penicillata*	Derivative	Seattle Genetics and Agensys	Approved by FDA	Metastatic urothelial cancer.	[160-162]
Glembatumumab vedotin CDX-011	*C. penicillata*	Derivative	Celldex Therapeutics Inc and National Cancer Institute (USA)	Phase II	Triple negative breast cancer, osteosarcoma, uveal melanoma, squamous cell carcinoma of the lung.	[163,164]
GSK2857916	*C. penicillata*	Derivative	GlaxoSmithKline	Phase II	Multiple myeloma.	[165-166]
Indusatumab vedotin	*C. penicillata*	Derivative	Takeda Oncology	Phase II	Gastrointestinal cancer; pancreatic cancer; colorectal cancer.	[167]
Ladiratuzumab vedotin	*C. penicillata*	Derivative	Genentech; Merck & Co; Quantum Leap Healthcare Collaborative and Seattle Genetics	Phase II	Breast cancer.	[168]
Lifastuzumab vedotin	*C. penicillata*	Derivative	Genentech	Phase I/II	Ovarian cancer, non-aquamous non-small Cell lung cancer.	[169,170]
Pinatuzumab vedotin	*C. penicillata*	Derivative	Genentech	Phase II	Diffuse large B-cell lymphoma, Non-Hodgkin lymphoma; chronic lymphocytic leukemia.	[171-173]
Polatuzumab vedotin (Polivy™)	*C. penicillata*	Derivative	Genentech	Approved by FDA	Diffuse large B cell lymphoma.	[172-174]
Tisotumab vedotin (HuMax®-TF-ADC)	*C. penicillata*	Derivative	Genmab and Seattle Genetics	Phase II	Non-small cell lung cancer (NSCLC), Ovary, cervical, endometrium, bladder, prostate and esophagus cancer; squamous cell carcinoma of the head and neck.	[175-177]
Vandortuzumab vedotin	*C. penicillata*	Derivative	Genentech	Phase I	Prostate cancer.	[178]

these side-effects, ASG-15ME was deemed to have promising efficacy against urothelial cancer.[179]

Brentuximab vedotin is an Antibody-Drug Conjugate (ADC) that was developed from dolastatin 10.[180] Brentuximab vedotin underwent multiple clinical studies from 2009 to 2016.[180] Peripheral neuropathy was recognized as the most common toxicity associated with Brentuximab vedotin. Moreover, nausea, fatigue, neutropenia, diarrhea, pyrexia, vomiting, arthralgia, pruritus, myalgia, peripheral motor neuropathy, and alopecia have also been identified as common Brentuximab vedotin-induced adverse drug reactions.[180] Despite these concerning side effects, Brentuximab vedotin was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use against Hodgkin Lymphoma (HL) in 2012 due to its high efficacy and it is currently in clinical use.[156]

Denintuzumab mafodotin is a novel Antibody-Drug Conjugate (ADC), which is linked to the microtubule-disrupting agent, Monomethyl Auristatin F (MMAF), a derivative of the natural compound auristatin (which was isolated from the cyanobacterium *C. penicillate*) against large B cell-non-Hodgkin lymphoma.[159] Denintuzumab mafodotin selectively targets CD19 protein, which is overexpressed in almost all B cell lymphomas.[157] In a dose escalation study, denintuzumab mafodotin was intravenously administered to sixty-two patients weekly for three weeks at 0.5-6 mg/kg, and then every six weeks thereafter at 3 mg/kg doses. Interestingly, thirteen of the fifty-five patients achieved complete remission, whilst a further seven patients achieved a partial remission. However, denintuzumab mafodotin has been associated with substantial side-effects including blurry vision, dry eye, fatigue and keratopathy, constipation, photophobia and nausea, although these toxicities are considered to occur at relatively low rates. Denintuzumab mafodotin is currently undergoing phase II clinical trials.[157-159]

Glembatumumab vedotin, is an antibody-drug conjugated to monomethyl auristatin E (MMAE), which is derived from the natural compound auristatin.[163] Glembatumumab vedotin selectively targets type IA transmembrane glycoprotein NMB.[163,164,181,182] The GNMB proteins are overexpressed in several cancer types including brain, breast, melanoma, lung osteosarcoma and hepatic cancers.[181,182] The first phase I/II clinical trials of glembatumumab vedotin tested the drug in patients with advanced melanoma. Five of the forty patients that participated in the clinical trial exhibited partial remission, and the further development of cancer was inhibited in twenty-seven patients at the end of the treatment cycle.[163] However, during the glembatumumab vedotin phase II clinical trial, only one of twenty-two osteosarcoma patients in that study achieved partial remission. The most common adverse effects were rashes. However, due to its relatively low efficacy against osteosarcomas, the next stages of clinical evaluations of glembatumumab vedotin were halted.[182] Glembatumumab vedotin has also been explored for anti-tumour activity against GNMB expressing Triple-Negative Breast Cancer (TNBC) in phase IIB trials to compare its efficacy with that of capecitabine. Multiple adverse effects including neutropenia, fatigue, diarrhea, rash and leukopenia were observed in all glembatumumab vedotin clinical studies.[181] Ongoing trials of glembatumumab vedotin against advanced melanoma are currently ongoing due to its promising anti-tumour activity and tolerable adverse effect profiles.[163]

Enfortumab vedotin is currently being developed as a selective inhibitor of nectin-4, a type I transmembrane polypeptide of nectin family.[183] Nectin-4 is overexpressed in several human malignancies including bladder, breast, lung and pancreatic cancers, and has a low expression in normal human tissues.[183] Despite toxicities including rash, fatigue, peripheral neuropathy, alopecia, decreased appetite, decreased hemoglobin levels, diarrhea, nausea, weight loss, and dry skin, enfortumab vedotin, received accelerated approval by FDA in 2019 for the treatment of patients with advanced bladder cancer[184-186] Enfortumab vedotin displayed excellent efficacy in all clinical trial phases.[160,161,184-188] Moreover, it is effective in treating urothelial cancer patients with decreased kidney function and diabetes.[160,161,184-188] Despite its side-effects, polatuzumab vedotin received accelerated approval by FDA in 2019 to treat adults with relapsed or refractory diffuse large B-cell lymphoma because of its high efficacy.[173]

Future directions and recommendations

Drug discovery from cyanobacteria has been limited to only a few species and there are many unexplored and underexplored species that may also have promising therapeutics properties and manageable side-effects.[189-201] To date, most research has focused on cyanobacterial species isolated from marine environments and that is limited to a handful of cyanobacteria genera. Freshwater and brackish water cyanobacterial species have received little previous attention in drug discovery despite being readily available and easily accessible. *Microcystis, Cylindrospermopsis* and *Spirulina* are amongst cyanobacterial genera that have received little interest to date in cancer drug discovery research. These cyanobacterial genera have high potential in cancer drug discovery.[189-201] Species from these genera are a rich source of cytotoxic compounds including anabeanopeptins, cyanopeptilons, microginis, microviridins, micropeptins, calcium-spirulan, nostosins and aeruginosins, phycocyanin.[189-201] All of these species have been poorly screened for the presence of potent anti-proliferative compounds. Indeed, these unexplored and underexplored cyanobacteria species may produce cytotoxic compounds that may be good leads for cancer drug development.

To date, more than 2000 cyanobacteria-derived bioactive compounds have been identified and isolated.[202] However, only a handful of these have been extensively screened for their therapeutic properties.[203] Instead, the majority of the

identified compounds are added to databases without rigorously exploring their therapeutic potentials, particularly as cancer drug leads. Identification and isolation of new compounds is costly, tedious and time consuming.[203] Despite this, comprehensive screening of identified and isolated natural products is vital to develop new drug leads, concurrently with studies screening for new compounds. These compounds may ultimately provide a potential pipeline for future cancer drug discovery. The success already achieved over the past decades highlights the need for substantially more screening of cyanobacterial metabolites as cancer drugs.

CONCLUSION

Cancer is one of the most concerning diseases globally, resulting in high mortality numbers, as well as placing a high burden on the health system. Current anticancer chemotherapeutic drugs have relatively high incidences of negative side effects, affecting not only the targeted cancer cells, but also normal cells. Additionally, many potential anticancer drugs have relatively low efficacy. Due to the costs and labour associated with anti-cancer drug production and discovery, the supply of these drugs is currently insufficient to meet the growing demand. These issues highlight the need to develop safe and novel anti-tumour products that can be produced for relatively low costs. New cancer chemotherapeutics should be highly effective and safe. Ideally, they should target novel mechanisms to be effective against cancers that are recalcitrant to current therapies that target specific cellular components and/or mechanisms. To date, most research to develop new anticancer drugs has focused on discovery of novel compounds from natural sources, including from bacteria and plants.[204] Multiple recent studies have demonstrated that cyanobacteria are also promising targets for the discovery of new therapeutic compounds.[203] Indeed, cyanobacteria have a wide range of anti-malignant properties. Additionally, their ability to grow in simple inorganic media at lower cultivation costs, as well as their rich diversity of bioactive metabolites, make them promising candidates for drug discovery. *Anabaena, Nostoc, Oscillatoria, Lynbgya, Leptolynbgya, Moorea, Symploca, Cyanobacter, Schizothrix, Phormidium, Dichothrix, Rivularia* and *Tolypothrix* have already been explored for the production of potent anticancer compounds.[203] Cyanobacterial dipeptides, depsipeptides, cyclic depsipeptides, linear peptides, cyclic peptides, lipopeptides, macrolides, indolophenanthridines, swinholides, macrolactones, polyphenols, alkaloids, lactones, fatty acids, terpenoids, polyketides, pyrroles and porphyrins are promising drug targets for the treatment of some cancers.[31] Dolastatins, lyngbyastatin, aurilide, cryptophycin, apratoxins and tolyporphin have proven to be effective in clinical trials and some these compounds have already been approved for clinical usage. However, in regards of cyanobacteria-derived cancer drug discovery, relatively few species have been thoroughly investigated and many of the previously identified compounds are yet to be rigorously screened for anti-cancer bioactivities. Substantially more research is required in this field.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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