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REVIEW ARTICLE

Cytotoxicity of bioactive compounds derived from cyanobacteria

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Abstract

Cyanobacteria are rich in bioactive compounds that exhibit diverse biological activities, including antiproliferative, cytotoxic, and antineoplastic properties. Many of these compounds are currently being studied in clinical trials. In this paper, newly discovered bioactive compounds from various cyanobacteria species that have demonstrated anticancer effects against multiple cancer cell lines, such as apratoxin, symplostatin 1, bartolosides, caylobolide, bisebromoamides, carmaphycins, and anaenamides, are reviewed. At present, there are no clear guidelines on approving cyanobacteria-derived bioactive compounds for use in treating diseases. While it is not uncommon that the intake of these compounds is accompanied by side effects, investigations on these compounds should focus on increasing the safety and efficacy of the compounds, or at least tread a fine line between drug safety and effectiveness for cancer patients. This review overviews the efficacy and cytotoxicity of cyanobacteria-derived bioactive compounds, providing researchers insights into how to maximize the benefits of these compounds through research.

Keywords: Bioactive compounds; Cyanobacteria; Cytotoxicity

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1. Introduction

Cancer is the leading cause of death worldwide, resulting in approximately 10 million deaths in 2020.In addition, there were 19.3 million new cases reported[1]. There are over 200 types of cancer that can spread throughout the body, leading to metastasis and potentially fatal consequences[2]. Many chemotherapy drugs used to fight cancer can harm both cancerous and healthy cells. Natural compounds derived from natural sources, such as marine organisms, plants, and microorganisms, have become popular therapeutic candidates for treating cancer because they can effectively target cancer cells with little to no harmful effects on healthy cells[3,4]. Cyanobacteria, also known as blue-green microalgae, contain a variety of bioactive compounds with low to high molecular weight, such as hapalindole A, oscillapeptin A, minutissamide A, lyngbic acid, caylobolide B, anabaenopeptin E, lobocyclamides, lyngbyacyclamides A and B, homodolostatin, malyngamides, glicomacrolides, swinholides, macrolactones, and viridamides. Approximately 40% of these compounds can be utilized as anticancer and antimicrobial agents[5,6], and most of these compounds are currently under clinical investigations[7]. Cyanobacteria-derived bioactive compounds have shown promising anticancer activity against cancer cells. This can be attributed to various mechanisms, such as inducing cell cycle arrest in the G1 phase, inhibiting serine proteases such as

elastase and trypsin, causing DNA fragmentation and oxidative stress, disrupting microfilaments, modulating Bcl-2 protein, and even modifying cell membrane dynamics (Figure 1)[8,9]. In this review, the potential cytotoxicity of compounds derived from cyanobacteria is discussed.

2. Cyanobacteria

Cyanobacteria is a Gram-negative prokaryote rich in the pigment c-phycocyanin and is capable of oxygenic photosynthesis[10]. Cyanobacteria can be found in different environments, such as oceans, freshwater, bare rock, and soil, and can survive in extreme high-temperature conditions, such as geothermal and hot spring water[11]. Cyanobacteria exist as individual cells (Spirulina), filaments (Oscillatoria), or colonies (Nostoc) enclosed by a mucilaginous sheath. Cyanobacteria are typically microscopic but become visible when they form colonies[12]. The classification of cyanobacteria was proposed in 1985, and it was initially classified into four orders: Nostocales, stigonematales, chroococcales, and oscillatoriales. At present, there are five orders of cyanobacteria, namely, pleurocapsales, chroococcales, stigonematales, nostocales, and oscillatoriales (Table 1)[13].

Cyanobacteria are known to contain a variety of bioactive compounds, such as peptides, polyketides, terpenes, alkaloids, fatty acids, and ultraviolet-absorbing compounds. The biosynthesis pathways of these compounds are illustrated in Figure 2. These bioactive compounds are produced through both non-ribosomal (non-ribosomal peptide synthetases) and ribosomal pathways. Polyketide metabolites, for instance, contain cis- and trans-acyltransferases, with the trans-face having non-repetitive acyltransferases and the cis-face having repetitive acyltransferases[14]. There are several traditional extraction methods used to extract bioactive compounds from different marine sources (such as cyanobacteria). The traditional methods include Soxhlet extraction (extract organic compounds such as phenols, pesticides, and polycyclic aromatic hydrocarbons), hydrodistillation, hot continuous extraction, percolation, maceration, infusion, and decoction. In contrast, modern extraction methods include supercritical fluid extraction, microwave-assisted extraction, pressurized liquid extraction, and enzyme-assisted extraction[15].

3. Anticancer compounds from cyanobacteria

Cyanobacteria contain a variety of anticancer drugs, which are reviewed in the following sub-sections.

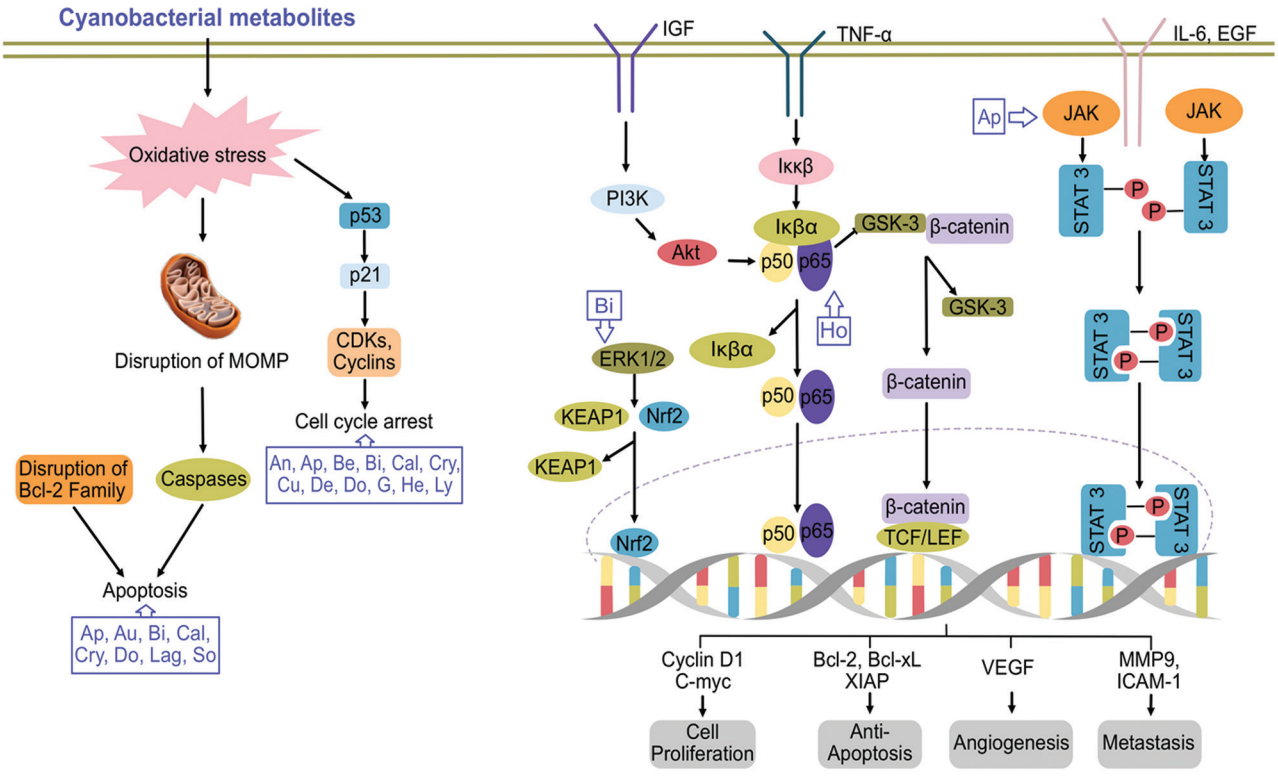


Figure 1. Potential anticancer mechanisms of bioactive compounds derived from cyanobacteria. Adapted from Qamar *et al.*[9], distributed under Creative Commons Attribution (CC BY) license.

Table 1. Classification of cyanobacteria[13]

No.	Order	Species	Environment	Morphology
1	Nostocales	*Anabaena* sp.	Freshwater	Filamentous
		Nostoc sp.		Terrestrial
2	Chroococcales	*Microcystis* sp.	Freshwater	Unicellular
		Synechococcus sp.	Marine water	
		Synechocystis sp.	Freshwater	
3	Pleurocapsales	*Hyella caespitosa*	Marine water	Unicellular
4	Stigonematales	*Fischerella muscicola*	Freshwater	Filamentous
5	Oscillatoriales	*Oscillatoria* sp.	Freshwater	Filamentous
		Lyngbya majuscula	Tropical marine water	

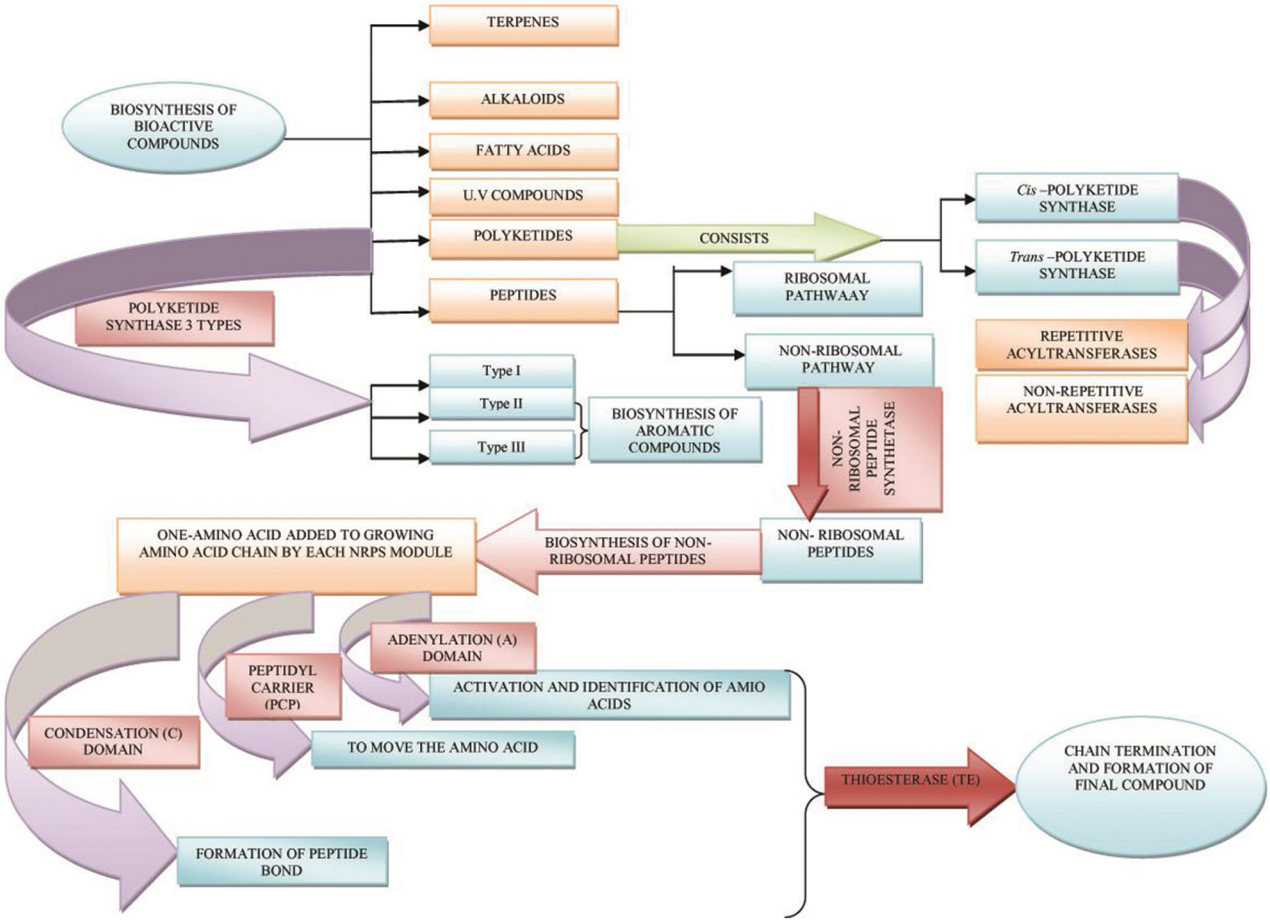


Figure 2. Biosynthesis pathway of the cyanobacteria bioactive compounds. Adapted from Pattnaik and Singh, 2020[14], distributed under a Creative Commons Attribution (CC BY) license.

3.1. Cyclic depsipeptides

3.1.1. Apratoxin

Apratoxin A is a new potent cytotoxic compound derived from marine cyanobacteria *Lyngbya majuscula*. Apratoxin A is a cyclic depsipeptide made up of R (â-unsaturated modified cysteine residues), proline, 3-dihydroxyliety fatty acid, 7-dihydroxy-2,5,8,-tetramethylnonenoic acid, and 3-methylated amino acids (O-methyltyrosine, N-methyl isoleucine, and N-methyl-alanine)[16] (Figure 3). Apratoxin A exhibited significant cytotoxicity against KB (0.52 nM) and colon LoVo (0.36 nM) cancer cells. *In vivo*

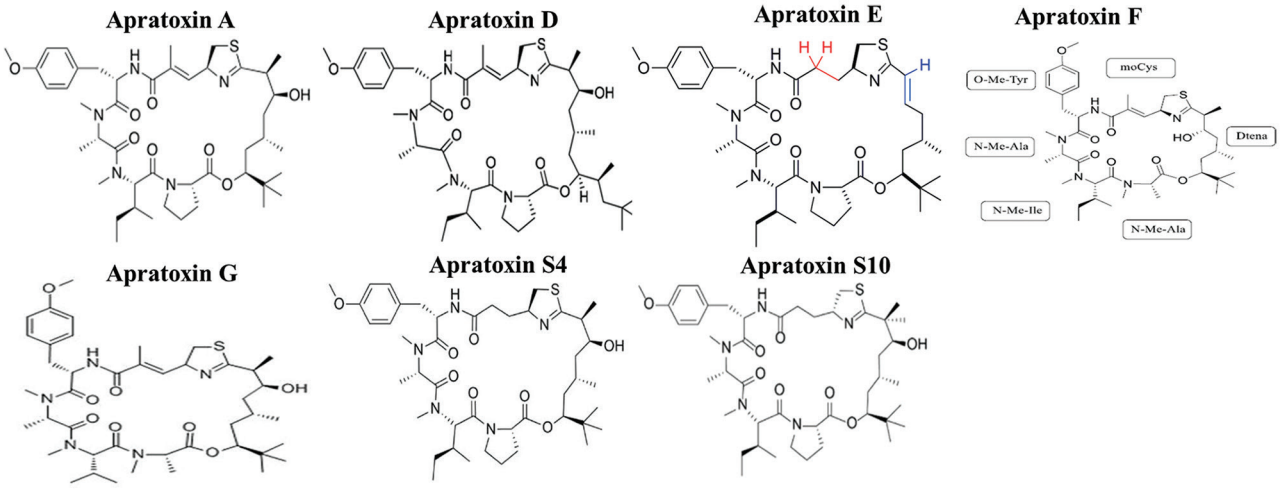


Figure 3. Chemical structure of apratoxin and its analogs.

testing demonstrated that apratoxin A induced moderate tumor inhibition on day 9, with a T/C ratio of 51%, and a weight loss of 21%. However, by day 23, complete recovery was observed, indicating a lengthy recovery period of 14 days[17]. Apratoxins have been found to exhibit strong anticancer activity through the down-regulation of receptor tyrosine kinases and their ligands, including interleukin-6 and vascular endothelial growth factor A (VEGF-A). This is achieved through the blocking of a specific stage of secretory pathways, namely, cotranslation on the Sec61 channel[18].

Apratoxin D (Figure 3) is a cyclodepsipeptide extracted from *Lyngbya sordida* and *L. majuscula*. Its structure is similar to apratoxin A but contains a polyketide carbon chain of 3,7-dihydroxy-2,5,8,10,10-pentamethylundecanoic acid. Apratoxin D has been found to have potent anticancer effects against H-460 cells, a human lung cancer cell line, with a half maximal inhibitory concentration (IC_{50}) of 2.6 nM[19,20]. Apratoxin E, isolated from *Lyngbya bouillonii*, is a polypeptide domain that is similar to apratoxin A. Apratoxin E is known for its potent cytotoxic effects on various cancer cell lines, such as cervical cancer cells (HeLa), human osteosarcoma cells (U-2 OS), and human colorectal adenocarcinoma cells (HT29). Its IC_{50} values for HeLa, U-2 OS, and HT29 cells are 72, 59, and 21 nM, respectively[21,22].

Apratoxins F and G are also derived from *L. bouillonii*. The polyketide moiety in apratoxins G and F is similar to that in apratoxin A (Figure 3). However, apratoxins F and G possess an N-methyl alanine unit in place of a proline unit in apratoxins A to E. Apratoxins G and F exhibited high cytotoxicity to H-460 cells with IC_{50} of 14 and 2 nM, respectively[19,21]. Apratoxin H and apratoxin A sulfoxide are derived from *Moorea producens*. Apratoxin H has pipecolic acid instead of the proline residue found in apratoxin A. Meanwhile, apratoxin A sulfoxide differs from apratoxin A in terms of the degree of oxidation. Both apratoxin H and apratoxin A sulfoxide exhibited cytotoxicity against H460 cells, with IC_{50} values of 3.4 and 89.9 nM, respectively[23]. Apratoxin S4 and S10 (Figure 3) are novel Sec61 inhibitor that blocks the translocation of secretory proteins into the endoplasmic reticulum. Apratoxin S4 and S10 are cytotoxic to pancreatic cells and suppress the overall secretion from pancreatic cancer cells by inhibiting cytokines from stromal cells or reducing the level of factors secreted by other cells[18,24]. This difference in the anticancer activity of apratoxin and its analogs might be due to the differences in their structure and stability.

3.1.2. Cocosamides

Cocosamides A and B, obtained from *L. majuscula*, are cyclic depsipeptides consisting of six amino/hydroxy units, including proline, NMe-Phe (two units), 2,2-dimethyl-3-hydroxy-7-octenoic acid (Dhoea), or a β-amino acid of 2,2-dimethyl-3-hydroxy-7-octynoic acid (Dhoya), glycine, and valine (Figure 4). These compounds exhibit moderate cytotoxicity against MCF-7 cancer cells (IC_{50} between 30 and 39 mM,) and HT-29 cells (IC_{50} between 24 and 11 mM)[19,25].

3.1.3. Aurilides

Aurilides are a type of cyclic depsipeptides. They contain a α-hydroxy-acid residue, a pentapeptide, and a polyketide fragment with three or four stereogenic centers (Figure 4). These compounds are isolated from *L. majuscula*. Two specific types, aurilides B and C, have demonstrated high levels of cytotoxicity against NCI-H460 (50% lethal

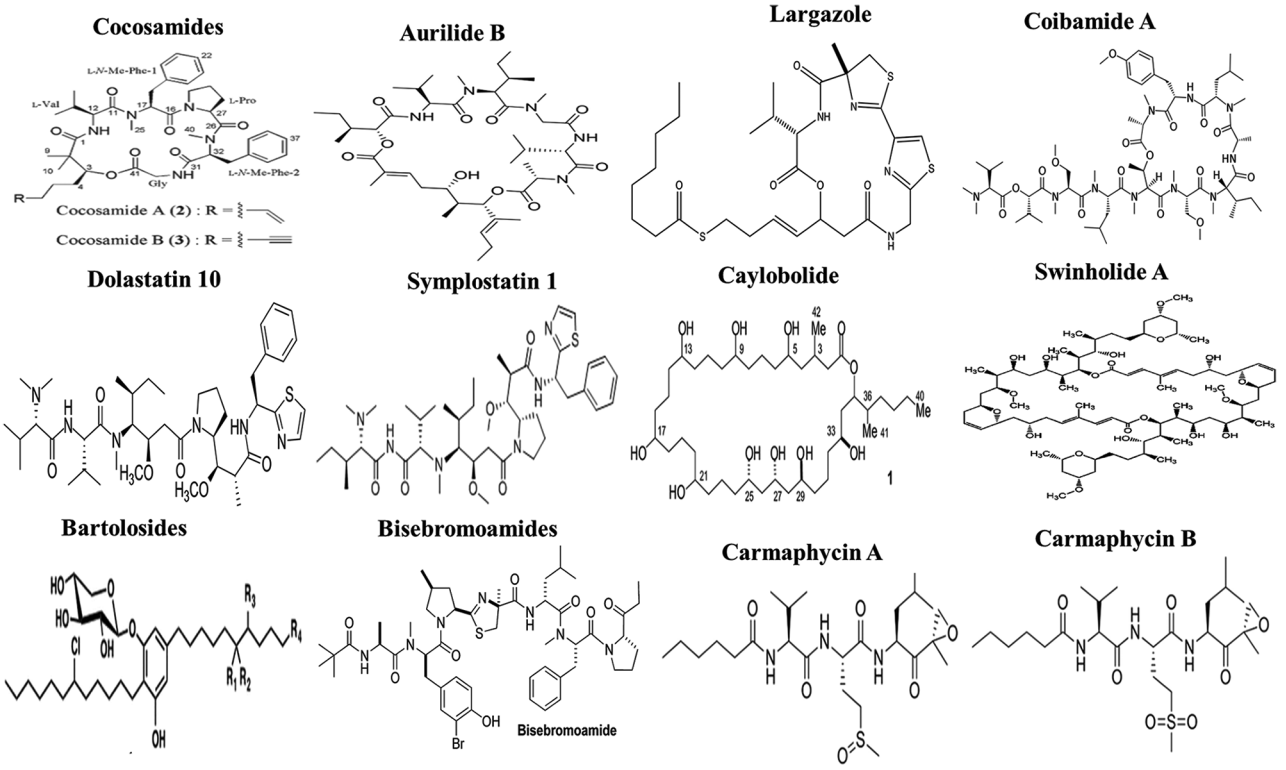


Figure 4. Chemical structure of cocosamides, aurilide B, largazole, coibamide A, dolastatin 10, symplostatin 1, caylobolide, swinholide A, bartolosides, bisebromoamides, carmaphycin A, and carmaphycin B.

concentration [LC_{50}] of 40 and 130 nM) and Neuro-2a mouse neuroblastoma cells (LC_{50} of 10 and 50 nM), respectively[9,26,27].

3.1.4. Largazole

Isolated from *Symploca* spp., Largazole (Figure 4) is a potent histone deacetylase inhibitor. These compounds showed anticancer activity against various cancer cell lines such as HCT-116 (GI_{50} = 80 nM), MDA-MB-231 (GI_{50} = 7.7 nM), HT-29 (GI_{50} = 12 nM), U-2 OS (GI_{50} = 55 nM), SK-OV-3 ($IC5_0$ = 250 nM), IMR-32 (GI_{50} = 16 nM), A549 (GI_{50} = 320 nM), HeLa (IC_{50} = 170 nM), Eca-109 (IC_{50} = 100 nM), Bel 7402 (IC_{50} = 170 nM), U937 (IC_{50} = 20 nM), 797 (IC_{50} = 24 nM), 10326 (IC_{50} = 25 nM), PC3 (IC_{50} ≤ 500 nM), LNCap (IC_{50} ≤ 500 nM), panel of melanoma cell lines (IC_{50} = 45-315 nM), NCI-H1975 (IC_{50} = 83 nM), NCI-H460 (IC_{50} = 120 nM), GLC-82 (IC_{50} = 190 nM), L78 (IC_{50} = 570 nM), SPC-A1 (IC_{50} = 140 nM), 95D (IC_{50} = 420nM), NCI-H466 (IC_{50} = 520 nM), SW620 (IC_{50} = 26.5 nM), MiaPaCa (IC_{50} = 206.4 nM), SH-SY5Y (IC_{50} = 102 nM), SF-268 (IC_{50} = 62 nM), and SF-295 (IC_{50} = 68 nM). This compound suppresses cancer probably by virtue of its ability to modulate cell cycle and antagonize AKT, KRAS, and HIF[19,28].

3.1.5. Coibamide A

Coibamide, a cyclic depsipeptides cyanotoxin derived from *Leptolyngbya* sp., has been found to have a significant impact on various types of cancer cells. In a dose-dependent manner, coibamide increases the percentage of NCI-H460 cells and mouse Neuro-2a cells in the sub-G1 population. In addition, it has been demonstrated to arrest the cell cycle of NCI-H460, Neuro-2a cells (LC_{50} = 23 nM), MDA-MB-231, melanoma LOX IMVI, NCI-60 (GI_{50} between 0.4 and 7.6 nM), astrocytoma SNB75, and leukemia HL-60 in the G1 phase.

The anticancer effect of coibamide A (Figure 4) is distinctly mediated through the activation of caspase 3 (in SF-295 cells) to induce apoptosis or the activation of autophagy via an mTOR-independent mechanism (in U87-MG cells). It also prevents autophagosome-lysosome binding in MDA-MB-231 cells through protein glycosylation modification-lysosome membrane (LAMP1 and LAMP2). Moreover, it reduces VEGFR2 expression and inhibits VEGF-A secretion in MDA-MB-231 and U87-MG cells. Coibamide A also decreases the expression of human epidermal growth factor receptor receptor in non-small cell lung and breast cancer cells. The effectiveness of coibamide

in fighting cancer makes it a promising candidate for further study and development[29-34].

3.2. Cyclic peptides and depsipeptides

3.2.1. Dolastatins

Dolastatins represent a group of cyclic and linear peptides, depsipeptides, and macrolides, containing oxazole heterocycles and thiazole. These peptides are derived from *Symploca sp*. Dolastatin 10 and 15 (Figure 4) can depolymerize microtubules and are also capable of inducing apoptosis by arresting the cell cycle in the G2/M phase of various cancer cell lines, including A549, KB, DU-145, and LoVo cells. Their IC_{50} values are 0.97, 0.052, 0.5, and 0.076 nM, respectively[9].

3.2.2. Symplostatin 1

Symplostatin 1 (Figure 4), a dolastatin 10 analog derived from marine cyanobacteria *Symploca hydnoides*, is shown to possess potent cytotoxic effects against MDA-MB-435 (breast cancer) and ovarian cancer cell lines (IC50 of 0.15 and 0.09 nM, respectively). An *in vivo* study revealed that symplostatin 1 can effectively suppress the growth of murine mammary 16/C and murine colon 38 cell lines, which took a longer time for the cells to recover from toxicity[35].

3.3. Macrolides

3.3.1. Caylobolide

Caylobolides (Figure 4) are macrolides (macrolactones) isolated from the *Phormidium sp.* and *L. majuscula*. Caylobolide A exhibited cytotoxic properties against HCT-116 cells (human colon tumor) with an IC_{50} of 9.9 μM[36], while caylobolide B showed anticancer activity against HeLa and HT-29 cells, with IC_{50} values of 12.2 and 4.5 μM, respectively[37].

3.3.2. Swinholide

Swinholide is a type of macrolide containing a unique, larger lactone ring structure known as a dimeric 44-membered ring (Figure 4). Swinholide A is derived from *Phormidium sp.* and has been found to possess anti-cancer properties against fibrosarcoma cells (HT-1080) and H-460, with IC_{50} values of 0.017 μg/mL and between 170 and 910 nM, respectively[28,38].

3.4. Glycolipids

3.4.1. Bartolosides

Bartoloside (Figure 4) is a newly discovered type of chlorinated aromatic glycolipid. It is composed of mono- and/or di-glycosylated dialkylresorcinols (DARs) with halogenated alkyl moieties. The marine cyanobacteria, *Synechocystis salina,* and *Nodosilinea sp.*, are the principal sources of this compound[28]. According to Afonso *et al.*,[39] Bartoloside A has been found to have anticancer effect on human osteosarcoma (MG-63), colon carcinoma (RKO), and human breast cancer (T-47D) cells, with IC_{50} values of 22, 40, and 23 μM, respectively.

3.5. Linear peptides

3.5.1. Bisebromoamides

Bisebromoamides are linear peptides (Figure 4) derived from *Lyngbya sp.* They are known to impair actin dynamics and have demonstrated anticancer properties against various cancer cell lines, including HeLa S3, JFCR39 (a panel of 39 human cancers)[40], NRK, 769-P, 786-O kidney cancer cells[41], and HCT-116 (with EC_{50} ranging between 45 and 483 nM)[42]. The compound showed an IC_{50} of 40 nM against HeLa S3 cells and a GI_{50} of 40 nM against JFCR39 cells[40].

3.5.2. Carmaphycins

Extracted from *Symploca* sp., carmaphycins A and B (Figure 4) are new forms of marine-based epoxyketone 20S proteasome inhibitors. These substances have demonstrated strong anticancer effect against NCI-H460, HCT-116, and the NCI-60 cell lines, with a GI_{50} range of 1 – 50 nM[43].

3.6. Depsipeptides

3.6.1. Anaenamides

Anaenamides A and B are new geometric isomers and linear depsipeptides derived from *Hormoscilla sp.* These compounds contain two α-hydroxy acid residues, an alkylated-salicylic fragment, and an abnormal α-chlorinated-α,β-unsaturated (E/Z) ester. Anaenamides A and B (Figure 4) were found to have mild anticancer properties against the HCT-116 cell line, with IC_{50} values of 4.5 and 8.7 μM, respectively[44]. Different from anaenamides A and B, anaenamides C and D possesses a primary amide instead of a methyl ester. However, anaenamides C and D have been demonstrated to display anticancer effect against HCT-116 cells at an IC_{50} of 100 μM but no cytotoxic activity against human embryonic kidney cells (HEK293)[44,45].

3.7. Linear lipopeptides

3.7.1. Almiramides

Almiramides are linear lipopeptides that are highly N-methylated. They are derived from *Oscillatoria nigroviridis* and *L. majuscula*. Almiramides B and D (Figure 5) have been found to display strong cytotoxic effects against MDA-MB-231, with an IC_{50} of 13 μM[46].

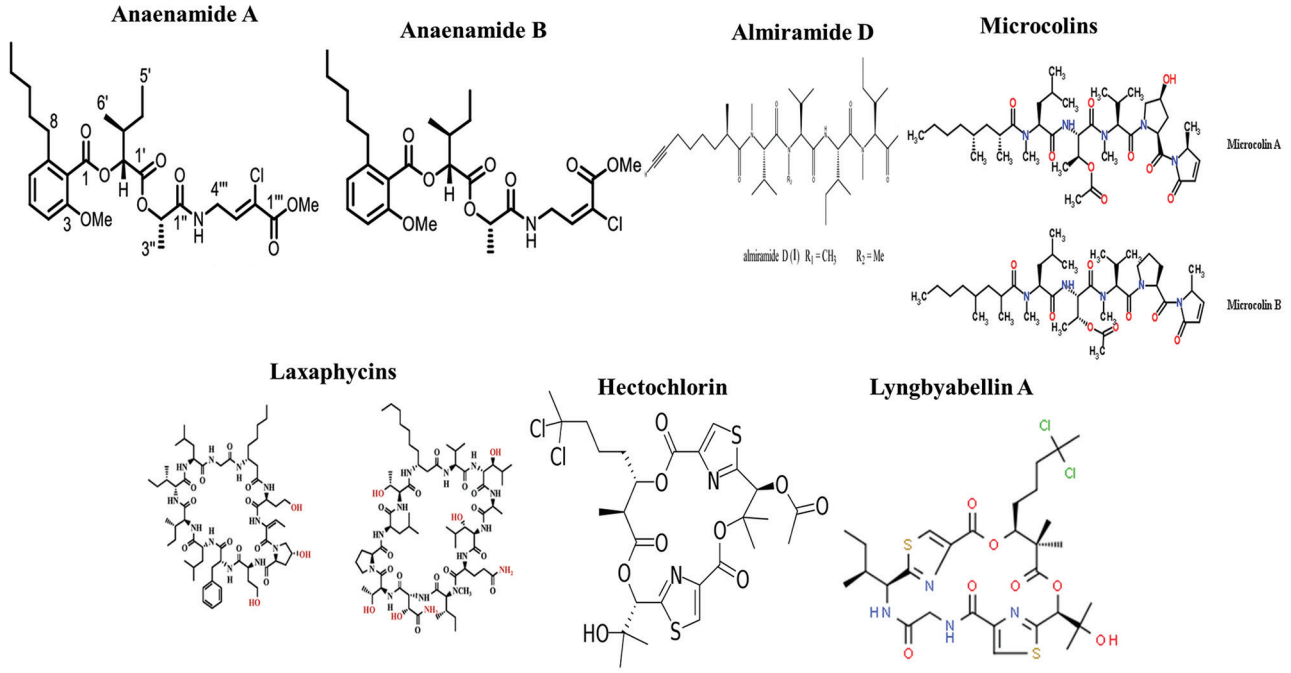


Figure 5. Chemical structure of anaenamide A, anaenamide B, almiramide D, microcolins, laxaphycins, hectochlorin, and lyngbyabellin A.

They also showed similar effects on HeLa cells, with an IC_{50} of 17 µM, and on other cells such as A549, HT-29, and PC3, with IC_{50} ranging from 18 to 107 µM[46].

3.7.2. Microcolins

Microcolins (Figure 5) are new linear lipopeptides, which are isolated from *L. polychroa* and *M. producens*. These lipopeptides have demonstrated powerful cytotoxicity against NCI-H460, with IC_{50} ranging between 6 nM to 1 µM[47]. In addition, microcolins A and B, along with deacetylmicrocolin B, have shown cytotoxicity against IMR-32 and HT-29, with IC_{50} between 0.28 and 14 nM[47,48].

3.7.3. Wenchangamides

Wenchangamide A is a lipopeptide recently discovered from the filamentous *Neolyngbya* sp. This compound has been found to have anticancer properties against HCT-116, with an IC_{50} of 38 µM[49]. It works by either arresting the cell cycle at the G2/M phase or inducing apoptosis. Importantly, wenchangamide A does not have any toxic effects on normal human dermal fibroblasts (NHDF), indicating that it specifically targets cancer cells[49].

3.8. Cyclic lipopeptides

3.8.1. Hectochlorins

Hectochlorins (Figure 5) are cyclic lipopeptides isolated from *M. producens*. Hectochlorins demonstrated potent cytotoxic activity against various types of cancer cells, including NCI-H 187, B lymphocyte CA46, and human mouth epithelial KB cells, with IC_{50} values of 1.2, 0.02, and 0.86 µM, respectively[50]. It has also been found to display high cytotoxicity to melanoma, colon, and kidney cancer cell lines, with a GI_{50} of 5.1 µM[51]. The previous studies also reported that hectochlorins are cytotoxic against NCI-H187 and KB cell lines, with IC_{50} values of 0.32 and 0.31 µM, respectively[50-52].

3.8.2. Laxaphycins

Laxaphycins (Figure 5) are cyclic-lipopeptides that are isolated from marine cyanobacterium *Hormothamnion enteromorphoides*. Laxaphycin B4 demonstrated cytotoxic effects against HCT116 cells with an IC_{50} of 1.7 µM[53]. Laxaphycin A2, on the other hand, showed low cytotoxicity with an IC_{50} of 2 µM[53,54].

3.9. Peptolides

3.9.1. Lyngbyabellins

Lyngbyabellins represent a group of cyclic depsipeptides and lipopeptides containing dichlorinated polyketide-derived moiety. Lyngbyabellins are isolated from *L. bouillonii* and *L. majuscula*. One of these compounds, lyngbyabellin A (Figure 5), showed moderate anticancer activity against KB and LoVo cell lines, with IC_{50} values of 0.03 µg/mL and 0.5 µg/mL, respectively[28]. However, *in vivo* studies have revealed that lyngbyabellin A is toxic to mice at concentrations between 0.01 and 5.0 µg/mL[55,56]. On

the other hand, lyngbyabellin B is more toxic to mice than lyngbyabellin A. In addition, lyngbyabellin E to I exhibited cytotoxicity against NCI-H460 and Neuro-2a cells, with LC_{50} values ranging from 0.2 to 4.8 μM[55]. Lyngbyabellin N has been shown to possess potent cytotoxicity against the HCT116 cell line, with an IC_{50} of 40.9 ± 3.3 nM[57]. However, lyngbyabellins K, L, M, and 7-epi-lyngbyabellin L did not show any toxic activity compared to other compounds[55-57].

3.9.2. Majusculamides

Majusculamide C and D (Figure 6) and desmethoxymajusculamide C are cyclopeptolides derived from the marine cyanobacterium *L. majuscula*. Majusculamide C demonstrated potent cytotoxicity against ovarian carcinoma (OVCAR-3), kidney cancer (A498), glioblastoma SF-295, NCI-H460, and colorectal cancer (KM20L2) cell lines with IC_{50} values of 0.51, 0.058, 0.013, 0.0032, and 0.0013 μg/mL, respectively[58]. Desmethoxymajusculamide C has been shown to display strong cytotoxicity against HCT-116, with an IC_{50} value of 20 nM[9]. Moreover, majusculamide D is cytotoxic to PANC-1, U251N, HepG2, NCI-H125, and P388, with IC_{50} values of 0.32, 36.8, 1396, 147, and 3.3 nM, respectively[58].

3.9.3. Patellamides

Patellamides (Figure 6) are cyclic octa-peptides containing thiazoles and oxazolines. These compounds are obtained from *Prochloron didemni*. Patellamides A, B, and C have been found to exhibit anticancer activity against the L1210 cell line, with IC_{50} values ranging from 2 to 3.9 μg/mL[59].

In addition, patellamide A has demonstrated cytotoxicity against acute CEM leukemia cells, with an IC_{50} of 0.028 μg/mL[28,59].

3.10. Polyketides

3.10.1. Aplysiatoxins

The aplysiatoxins (Figure 6) are polyketide metabolites derived from various types of cyanobacteria, such as *Oscillatoria sp.*, *L. majuscula*, *Lyngbya sp.*, *Schizothrix calcicola*, *Oscillatoria nigroviridis*, *Trichodesmium erythraeum*, and *M. producens*. Among these aplysiatoxins, some are new analogs such as neo-aplysiatoxin A, neo-debromoaplysiatoxin A, dolastatin 3, lyngbic acid, malyngamide M, hermitamide A, (−)-loliolide, and (+)-epiloliolide. These compounds have been found to be cytotoxic against mouse leukemia cells, with IC_{50} values ranging from 4.6 to 10 μg/mL[28,60].

3.10.2. Caldorazole

Extracted from *Caldora sp.*, caldorazole (Figure 6) has two thiazole rings and an O-methylenolpyruvamide moiety. This compound has been found to be effective against a few different cancer cell lines, such as CaSki and HT-1080 (with IC_{50} of 0.068 and 0.074 μM, respectively)[61]. It has also been shown to be cytotoxic against three types of HeLa cell lines (HeLa, HeLa S3Mer−, and HeLa S3), with IC_{50} values ranging from 0.023 to 0.048 μM[61]. The cytotoxicity of caldorazole might be executed through the inhibition of the activity of complex I in mitochondria; therefore, caldorazole is a promising selective targeting agent for cancer cells when glucose is restricted[61].

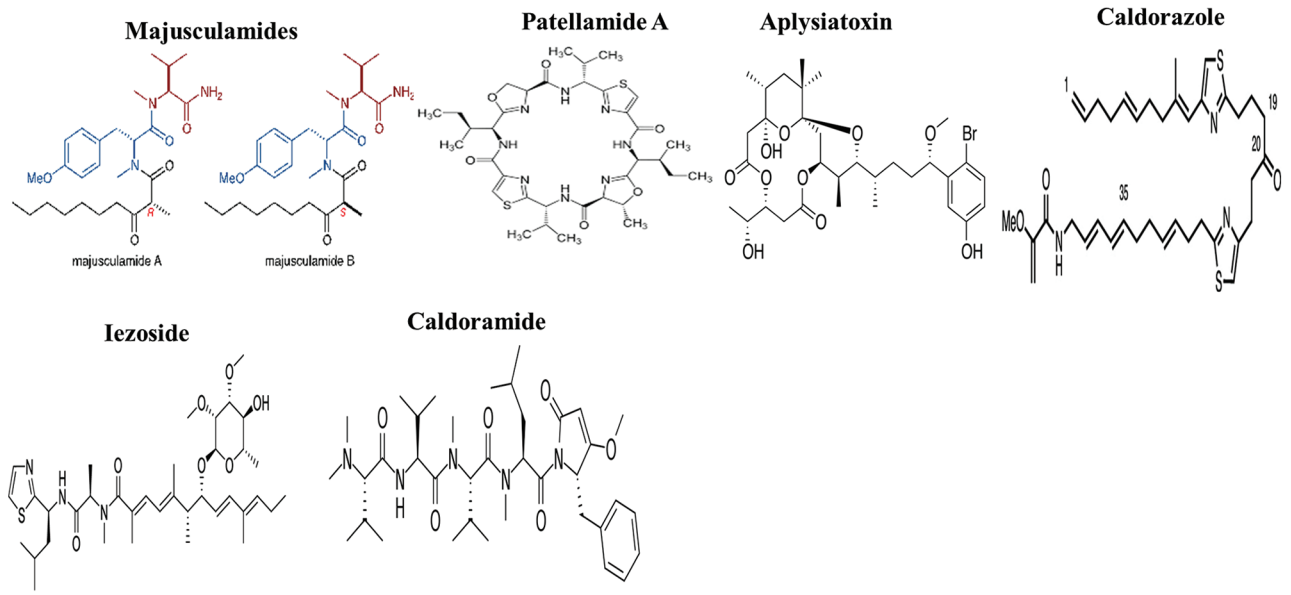


Figure 6. Chemical structure of majusculamides, patellamide A, aplysiatoxin, caldorazole, iezoside, and caldoramide.

3.11. Metabolites from other chemical families

3.11.1. Iezoside

A new compound called iezoside (Figure 6) is isolated from marine cyanobacterium *Leptochromothrix valpauliae*. It is a polyketide peptide with a unique structure that includes a 2,3-O-dimethyl-α-l-rhamnose branch, a conjugated diene group, and an α,β,γ,δ-unsaturated-amide group. Iezoside has been found to exhibit potent anticancer properties against HeLa cells with an IC_{50} value of 6.7 nM, causing a delay in the cell cycle, inducing morphological changes (spindle-like), and activating the apoptosis-induction pathways[62].

3.11.2. Caldoramide

Caldoramide (Figure 6) is a pentapeptide compound derived from the marine cyanobacterium *Caldora penicillata*. This compound exhibits potent cytotoxic activity against HCT116, HT-29, and MCF-7, with IC_{50} values of 43.8 ± 3.7, 77.5 ± 1.3, and 33.9 ± 1.3, respectively. However, its cytotoxicity is lower than that of belamide A and dolastatin 10[63].

Based on reviews in the literature, several compounds have been isolated from different cyanobacteria strains which may be due to the ability of cyanobacteria to produce these metabolites as a chemical defense technique against predators and compete for space and nutrients or to produce these metabolites when growing in extreme environment and/or cultivation under different cultivation condition or stress condition (such as high or low pH, temperature, and salinity).

Some metabolites have been found to exhibit cytotoxicity against different cancer cell lines, with varying cellular responses depending on the type of cancer cell. The mechanisms underpinning their cytotoxic effects include cell cycle arrest, caspase activation, impairment of the actin cytoskeleton, histone deacetylase inhibition, inhibition of the trimeric Sec61 translocon, depolymerization of microtubules, 20S proteasome inhibition, mitochondrial fragmentation, and prevention of multidrug resistance. Several other compounds are not reviewed in this paper due to a lack of information concerning their cytotoxicity or their selectivity toward normal cells rather than cancer cells. Therefore, modifying the structure of these compounds is necessary to create analogs that exhibit high cytotoxicity and are more selective against cancer cells than the original metabolite.

4. Conclusions

Cyanobacteria are known to contain various bioactive compounds, including apratoxin, symplostatin 1, bartolosides, caylobolide, bisebromoamides, carmaphycins, anaenamides, cocosamides, aurilides, wenchangamides, coibamide A, largazole, almiramides, dolastatins, microcolins, hectochlorins, lyngbyabellins, patellamides, majusculamides, aplysiatoxins, caldorazole, laxaphycins, iezoside, and caldoramide. These compounds can be found in various cyanobacteria species and have been shown to possess anticancer properties against a range of cancer cell lines, such as human colon carcinoma, osteosarcoma, breast cancer, lung cancer, cervical cancer, and fibrosarcoma cells. However, further research is needed to determine the safety and effectiveness of these compounds in animal models and clinical applications. It is of utmost importance to find the right balance between drug safety and effectiveness for these compounds in the treatment of cancer. Although the general rule of thumb is to discontinue any further investigations on the slightly effective compounds that elicit severe side effects, there are still no clear guidelines on whether effective compounds that can cause significant side effects should be approved for further studies. This uncertainty poses a challenge for drug developers in selecting the appropriate drugs that have the highest potential to maximize the overall patient outcome in cancer treatment.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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