Biomedicine & Pharmacotherapy 170 (2024) 115989

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Bioactive substances of cyanobacteria and microalgae: Sources, metabolism, and anticancer mechanism insights

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ARTICLE INFO

Keywords:
Microalgae
Cyanobacteria
Bioactive compounds
Cancer
Aquatic environment
Apoptosis
Tumor

ABSTRACT

Cyanobacteria and microalgae contain various phytochemicals, including bioactive components in the form of secondary metabolites, namely flavonoids, phenolic acids, terpenoids, and tannins, with remarkable anticancer effects. This review highlights the recent advances in bioactive compounds, with potential anticancer activity, produced by cyanobacteria and microalgae. Previous in vitro investigations showed that many of these bioactive compounds exhibit potent effects against different human cancer types, such as leukemia and breast cancers. Multiple mechanisms implicated in the antitumor effect of these compounds were elucidated, including their ability to target cellular, subcellular, and molecular checkpoints linked to cancer development and promotion. Recent findings have highlighted various mechanisms of action of bioactive compounds produced by

Abbreviations: G-Tags, Green carbon nanotags; HL-60, Human promyelocytic leukemia cells; Synechocystis, Cyanobacteria strain′; Synechococcus, Cyano-bacteria strain; Lyngbya majuscule, Cyanobacteria strain; Nostoc sp. GSV224, Nostoc strain GSV224; Apratoxin D, Anticancer compound from L. majuscula and L. sordida strains; MDA-MB-435, Breast carcinoma cell line; NCI/ADR, Ovarian carcinoma cell line; Leptolyngbya sp, Leptolyngbya strain; H-460, Lung cancer cell line; Symploca hydnoides, Symploca strain; MDA-MB-435, Breast cancer cell line; Bouillomides A and B, Compounds from Lyngbya bouillonii; Bcl-2, B-cell lymphoma 2; MEV, Mevalonate; IPP, Isopentenyl pyrophosphate; DMAPP, Dimethylallyl pyrophosphate; GPP, Geranyl pyrophosphate; FPP, Farnesyl pyrophosphate; GGPP, Geranylgeranyl pyrophosphate; TPS, Terpene synthase; HeLa, Human cervical cancer cells; HMG-CoA, 4-hydroxy-3-methyl-glutaryl-CoA; MCF-7, Breast cancer cell line′; MDA-MB-231, Breast-cancer cell line; IC50, Half maximal inhibitory concentration.

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https://doi.org/10.1016/j.biopha.2023.115989
Received 21 September 2023; Received in revised form 21 November 2023; Accepted 4 December 2023
Available online 15 December 2023

cyanobacteria and microalgae, including induction of autophagy and apoptosis, inhibition of telomerase and protein kinases, as well as modulation of epigenetic modifications. In vivo investigations have demonstrated a potent anti-angiogenesis effect on solid tumors, as well as a reduction in tumor volume. Some of these compounds were examined in clinical investigations for certain types of cancers, making them potent candidates/scaffolds for antitumor drug development.

1. Introduction

Microalgae, a unique group of photosynthetic microorganisms, have evolved a great diversity of biochemical compositions through their prolonged evolution [1]. They are classified into two distinct categories, including eukaryotic microalgae and prokaryotic (cyanobacteria). In recent years, over 50,000 species of microalgae were identified and investigated, with a proposed total number of species reaching 800,000 [2,3]. These microorganisms represent the most diverse group of living organisms, having colonized all niches of marine and terrestrial ecosystems. Their high ecological adaptability makes them an abundant source of useful and interesting components, being constantly exposed to various biotic and abiotic stressors [4,5]. Moreover, as photoautotrophs, their simple growth requirements and short life cycle make microalgae a potent source of high value-added biomolecules [5–7].

Microalgae are distinguished by their nutritional value and protein content, as well as richness in pigments, polyunsaturated fatty acids, polyphenols, polysaccharides, alkaloids, flavonoids, saponins, steroids, tannins, terpenes, and vitamins [8,9]. These compounds exhibit promising biological activities including anticancer, antioxidant, antimicrobial, anti-inflammatory, and immunomodulatory properties [4,5,10–14].

Procaryotic microalgae, namely cyanobacteria, represented by genera such as *Anabaena*, *Oscillatoria*, *Microcystis*, *Nodularia*, *Cylindrospermopsis*, *Calothrix*, *Symploca*, *Dichothrix*, *Leptolyngbya*, *Schizothrix*, *Geitlerinema*, *Aphanothece*, *Blennothrix*, and *Synechocystis* and *Lyngbya*, are known to synthesize a multitude of bioactive components [15–22]. Over 1600 molecules derived from cynaobacteria were identified, including linear decapeptides, acyclic peptides, cyclic depsipeptides, linear alkynoic lipopeptides, cyclic hexapeptides, cyclic undecapeptides, paracyclophanes, sesterterpenes, lipophylic cyclic peptides, polyphenolic ethers, glycolipids, and macrolactones [23]. These compounds exhibit a broad range of biological activities (antifungal, antiviral, cytotoxic, antibacterial, immunomodulatory, and protease inhibitor activities [17,18,20,21,24–26]. It is estimated that between 40,000 and 70,000 species of eukaryotic microalgae belong to different phyla, namely *Rhodophyta*, *Cyanophyta*, *Pyrrophyta*, *Chlorophyta*, *Haptophyta*, *Cryptophyta*, *Streptophyta*, and *Heterokontophyta* [2,3]. They possess a diversity of bioactive molecules, including carotenoids, phenolics, flavonoids, fatty acids, alkaloids, polysaccharides, vitamins, and lipids with promising antimicrobial, antioxidant, antitumor, anti-allergy, anti-inflammatory, and antiviral effectiveness [19,27,28].

Cancer is, along with cardiovascular disease (CVDs), remains one of the main factors of mortality in the world, with approximately 10 million deaths recorded in 2020. Despite the increasing availability of cancer therapies, many obstacles persist, such as the drug resistance, lack of selectivity towards specific emerging cancers, as well as the appearance of severe and undesirable side effects [14,29,30]. With this in mind, researchers are continually striving to discover new targeted therapies against human cancers, by exploring different sources, including natural products. During their 2.8 billion years of development, cyanobacteria have been subjected to multiple stresses, which have given them the ability to synthesize a diversity of bioactive molecules, some of which have demonstrated cytotoxic properties that can be exploited as anticancer agents. Numerous compounds demonstrating anti-cancer properties on various human cancer cell lines were discovered from cyanobacteria, some of them having even been the subject of clinical trials [31]. Cyanobacteria can synthesize many bioactive components with promising anticancer properties, targeting a variety of cancer cells [18,32–35]. These compounds act primarily by modifying cellular signaling pathway activation, inducing apoptosis, mitochondrial dysfunction, cell cycle arrest, and causing oxidative stress. Green carbon nanotags (G-Tags) derived from cyanobacteria showed potent cytotoxic activity related to their high solubility/photostability, low cytotoxicity, and multitarget capacity [36]. Studies have revealed membrane bud formation, cell shrinkage, and induction of apoptosis in HL-60 cells treated with aqueous extracts of the cyanobacteria (*Synechococcus* and *Synechocystis*) strains [37]. *Lyngbya majuscula* is a source of multiple chemicals with proven anticancer efficacy [23], including lyngbyastatin (an elastase inhibitor) [38], curacin A (a microtubulin inhibitor) [39], kalkitoxin (a sodium-channel blocker) [40,41], and cryptophycin (with antitumoral) [42]. Cryptophycin 1 (*Nostoc* sp. GSV224) was efficient against colorectal cancer and nasopharyngeal cancer cells, with 100–1000 times greater potency than currently available drugs. In addition, apratoxin D (*L. sordida* and *L. majuscula* strains) efficiently inhibited H-460 cells [43]. Similarly, symplostatin 1 (*Symploca hydnoides*) promoted suppression of breast cancer MDA-MB-435 cell and resulted in ovarian cancer (NCI/ADR) cell death [44]. As for coibamide (*Leptolyngbya* sp.), in MDA-MB-435 cells, it caused G_1 cell cycle arrest [45]. Finally, bouillomides B and A, extracted from *Lyngbya bouillonii*, showed remarkable efficacy in inhibiting the serine proteases elastase and trypsin [46]. Besides these properties, additional observations revealed induction of DNA fragmentation and oxidative stress, disruption of microfilaments, modulation of the protein Bcl-2 family, as well as dynamic alterations of cell membranes [47–49].

Cyanobacteria have previously given rise to commercial anticancer drugs [31], including dolastatin 10, bleomycin, santacruzamate A, and largazole, all classified as histone deacetylase (HDAC) inhibitors [50–52]. Many other anticancer drug candidates are also in development, going through preclinical stages to phase I to III trials [53–57]. Among these promising candidates, soblidotin has advanced to phase II trials due to its proven effectiveness against human colon adenocarcinomas. Moreover, synthadotin has demonstrated potent efficiency in phase II trials against inoperable [58].

Anticancer compounds derived from eukaryotic algae offer novel perspectives for the development of targeted cancer therapies, by modulating various mechanisms such as cellular cytotoxicity, induction of apoptosis and inhibition of invasion [59–62]. Microalgae, such as *Chaetoceros calcitrans, Skeletonema marinoi*, *Phaeodactylum tricornutum*, as well as the dinoflagellates *Amphidinium operculatum* and *Ostreopsis ovata*, have demonstrated potent effects on human cancer cells. Notably, fucoxanthin, a carotenoid, showed promising anticancer effect by inducing cell cycle arrest and cancer suppressor genes [63,64]. Additionally, ethanolic extracts of *Micractinium* sp. and *Chloromonas reticulata* have demonstrated growth-limiting effects on colon cancer cells and reduced expression of proinflammatory mediators in macrophages. As for *S. marinoi*, it has been shown to be effective against melanoma cells [65].

This review constitutes a synthesis of literature concerning the anticancer effect of bioactive molecules produced by cyanobacteria and eukaryotic microalgae. It focuses on molecules that have been extensively studied, highlighting their specific targets as well as the mechanisms underlying their anticancer activity.

2. Cyanobacteria as a source of bio-compounds

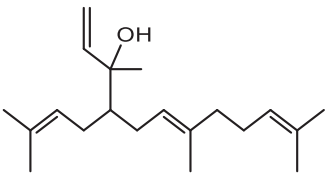
Cyanobacteria, due to their wide geographical distribution, can synthesize a wide range of secondary metabolites in order to cope with various possible environmental stresses. Among the most valuable bioactive substances identified in cyanobacteria are terpenoids, phenolic acids, flavonoids, alkaloids, vitamins, pigments, and polysaccharides (Table 1). These compounds give cyanobacteria a diversified biochemical potential and offer interesting opportunities for their use in different fields, particularly in pharmaceutical research and biotechnology.

2.1. Terpenoids

Terpenoids (or isoprenoids) play a central role in the production of chemical energy from light and in the maintenance of photochemical reactions, thus ensuring the development and survival of cyanobacteria. These compounds also play a major role in defense mechanisms and stress responses in plants [66,67]. Additionally, several terpenoids were discovered and exploited as anticancer drugs for various types of cancers [68]. Since cyanobacteria are photosynthetic, they are an excellent source of terpenoid production. Among the most investigated terpenoids of cyanobacteria are amorphadiene, farnesene, isoprene, beta-phellandrene, squalene, geranyllinalool, manoyl oxide, limonene, bisabolene, and farnesene (Fig. 1; Table 1). These compounds are synthetized by different species of cyanobacteria (*Synechocystis* sp., *Synechococcus elongatus*, *Synechococcus* sp., and *Anabaena* sp.).

Table 1
Bioactive compounds synthetized by cyanobacteria species.

Compounds	Cyanobacteria species	References
Terpenoid		
Squalene	*Synechocystis* sp.	[86]
Amorphadiene	*S. elongatus*	[87]
Farnesene	*S. elongatus* *Anabaena* sp.	[88,89]
Isoprene	*S. elongatus* and *Synechocystis* sp.	[90]
beta-phellandrene	*Synechocystis* sp.	[91]
Geranyllinalool	*Synechocystis* sp.	[92,93]
Manoyl oxide	*Synechocystis* sp.	
Limonene	*Synechocystis* sp., and *Synechococcus* sp.	[94,95]
Bisabolene	*Synechococcus* sp.	[94]
Phenolic acids		
Vanillic acid, ferulic acid, caffeic acid, gallic acid, and chlorogenic acid	*A. doliolum, O. acuta, P. boryanum,* and *H. intricatus*	[69]
Flavonoids		
Quercetin and lutein	*A. doliolum, O. acuta, P. boryanum,* and *H. intricatus*	[69]
Luteolin-7-glucoside and naringenin	*Leptolyngbyba* sp.	[96]
Rutin	*Microcheate tenera*	[71]
Alkaloids		
Hapalindoles	*H. fontinalis* and *F. muscicola*	[73] [74]
Ambiguine	*F. ambigua*	[75]
Fischerindole	*F. muscicola*	[76]
Vitamins		
β-carotene (pro-vitamin A)	*A. maxima, A. cylindrica*, and *Synechococcus* sp.	[79]
B2 (riboflavin), B5 (pantothenic acid), and B6 (pyridoxine)	*A. cylindrica*	[79]
Vitamin B12 (cobalamin), folic acid (B9), niacin (B3), and Riboflavin (B2)	*A. maxima* and *A. platensis*	[97]
B1 (thiamin)	*Nodularia spumegina*	[82]
C (ascorbic acid)	*A. cylindrica*	[79]
Polysaccharides		
Amylopectin	*Oscillatoria* sp.	[98]
Glycogen	*N. muscorum* and *A. nidulans*	[99];[100]
Maltose and a limit-dextrin	*S. platensis*	[101]
Other compounds		
C-phycocyanin	*A. platensis*	[84,85]



Geranyllinalool

Fig. 1. Chemical structures of terpenoids from cyanobacteria.

2.2. Phenolic acids

The synthesis of phenolic acids in cyanobacteria allows these photosynthetic microorganisms to tolerate and resist to various environmental stresses. In particular, accumulation of caffeic acid, gallic acid, vanillic acid, chlorogenic acid, and ferulic acid was found (Fig. 2; Table 1) when cultures containing cyanobacterial species, namely *Hapalosiphon intricatus, Plectonema boryanum, Oscillatoria acuta*, and *Anabaena doliolum*, were subjected to a significant amount of NaCl [69].

2.3. Flavonoids

Flavonoids play a central role in interfering with various signal transduction pathways involved in cancer development. They act by limiting cell proliferation, angiogenesis, and metastasis, while promoting apoptosis [70]. Cyanobacteria appear to be an excellent source of various flavonoids, particularly quercetin and lutin, produced by *H. intricatus, A. doliolum, O. acuta*, and *P. boryanum* [69], as well as luteolin-7-glucoside and naringenin produced by *Leptolyngbya* sp. [69], and rutin produced by *Microcheate acuta* [71] (Fig. 3; Table 1).

2.4. Alkaloids

Alkaloids are produced in response to stressors, whether of abiotic or biotic origin [72]. Cyanobacteria are known for their diverse production of indole alkaloids (Fig. 4; Table 1). Hapalindoles are produced by *Hapalosiphon fontinalis* [73] and *Fischerella muscicola* strains [74], while ambiguine is produced by *Fischerella ambigua* [75]. *F. muscicola* strains, on the other hand, produce fischerindole [76].

2.5. Vitamins

Photosynthetic organisms are frequently producers of vitamins. There are nine water-soluble vitamins, including the B vitamins such as vitamin B12 (cobalamin), folic acid (B9), biotin (B7), pyridoxine (B6), pantothenic acid (B5), riboflavin (B2), niacin (B3), and thiamin (B1), as well as vitamin C. The fat-soluble vitamins are A, D, E, and K. These vitamins are involved in the response to environmental stressors [77]. Nevertheless, not all plants are able to synthesize all the vitamins; in fact, vitamins K and D, as well as some forms of vitamin B, are rarely found in plants [78]. The production of vitamin D, K or B12 is restricted to cyanobacteria [78]. Among them, *Synechococcus* sp., *Anabaena cylindrica*, and *Arthrospira maxima* are distinguished by their high levels of β-carotene [79,80]. In freshwater and marine habitats, cyanobacteria play an essential role as the main suppliers of B vitamins. These water-soluble vitamins are exuded by strains of cyanobacteria, thereby benefiting other aquatic organisms [79,81,82]. B vitamins are also of crucial importance for the metabolic processes of cyanobacteria themselves [78], with high levels of vitamins B6, B5, and B2 observed in an aqueous strain of *A. cylindrica* [79], while a marine *A. cylindrica* strain produces significant amounts of vitamin B12. Moreover, *A. cylindrica* is

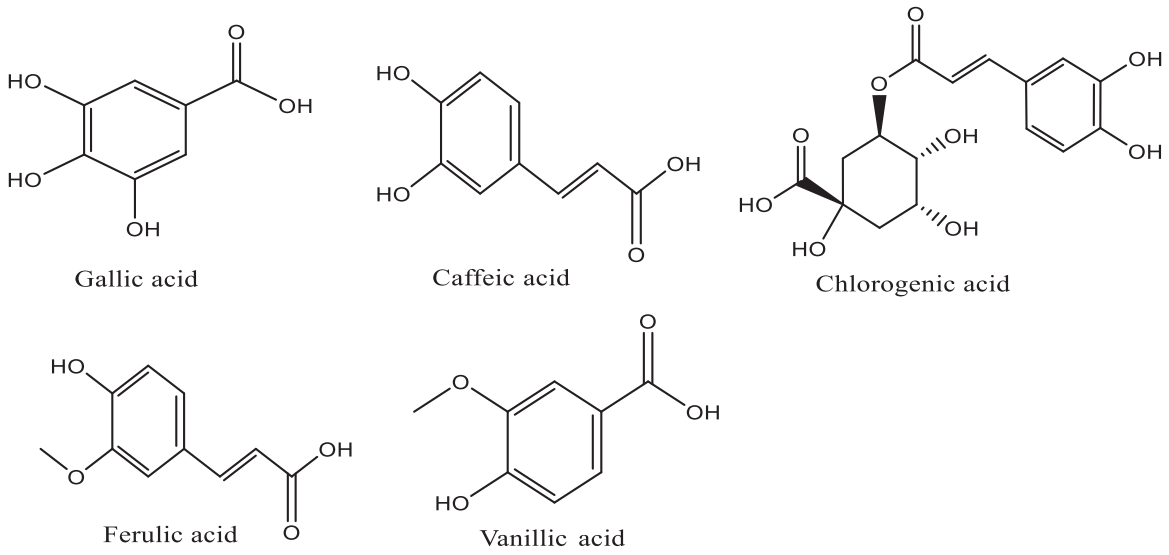


Fig. 2. Chemical structures of phenolic acids from cyanobacteria.

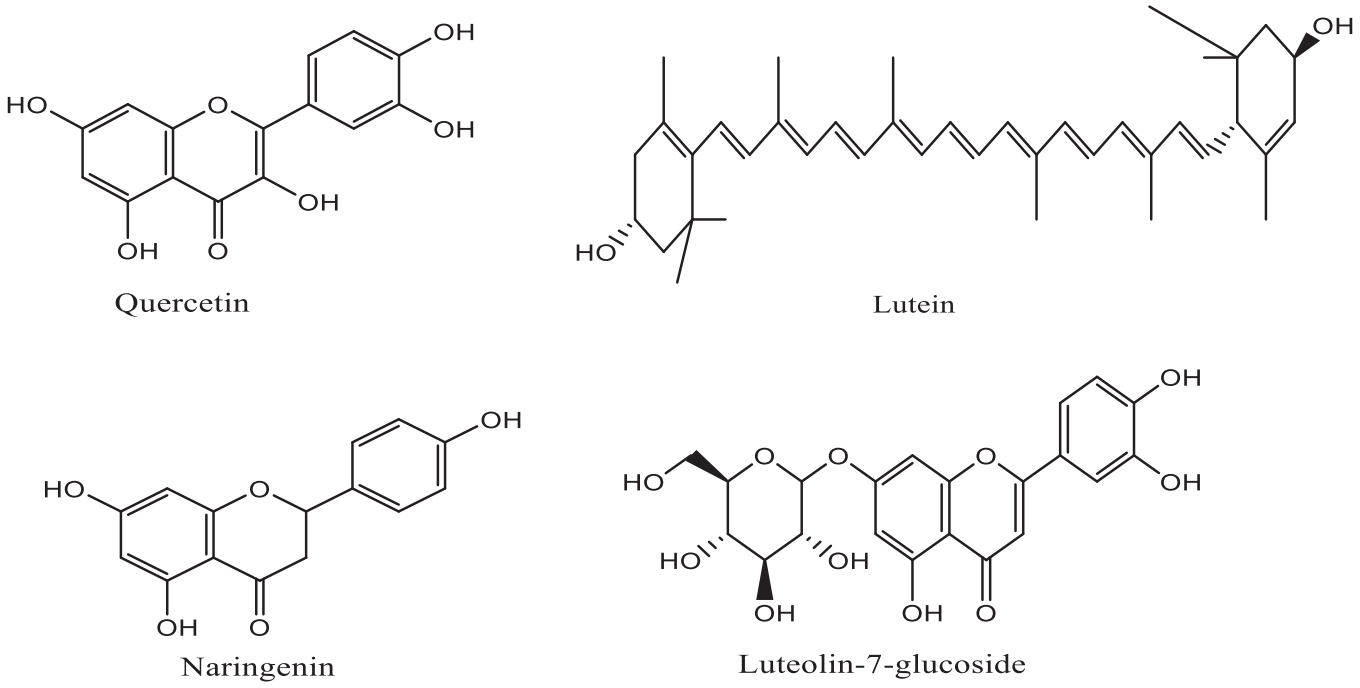


Fig. 3. Chemical structures of flavonoids from cyanobacteria.

also rich in vitamin C [79]. The vitamins synthetized by various cyanobacteria species are shown in Table 1.

2.6. Polysaccharides

Cyanobacteria produce many polysaccharides (PSs) that hold promising therapeutic potential with varied activities (Table 1). Several PSs, as well as their degraded and semi-synthetic derivatives, exhibit anticancer and preventive properties. They play a crucial role in restoring or maintaining the balance between apoptosis and proliferation, directly inhibiting tumor cells, as well as suppressing different phases of carcinogenesis and tumor growth. In addition to their low toxicity, accessibility, and suitability for oral administration, PSs possess a wide range of mechanisms of action, thus offering important nutritional and therapeutic benefits [83]. Among the cyanobacteria, *Oscillatoria* sp., *Nostoc muscorum*, *Anacystis nidulans*, and *Spirulina platensis* stand out as excellent sources of various PSs, such as amylopectin, glycogen, maltose, and dextrin.

2.7. Other compounds

C-phycocyanin, synthetized by *Arthrospira platensis* cyanobacterium strains, showed promising effect in treating cancer [84,85] (Table 1).

3. Microalgae as a rich source of bio-compounds

The alteration of environmental conditions as well as the absence or presence of specific substances can influence the production of certain compounds by microalgae. These metabolic changes allow microalgae to adapt to external environmental changes. Numerous investigations

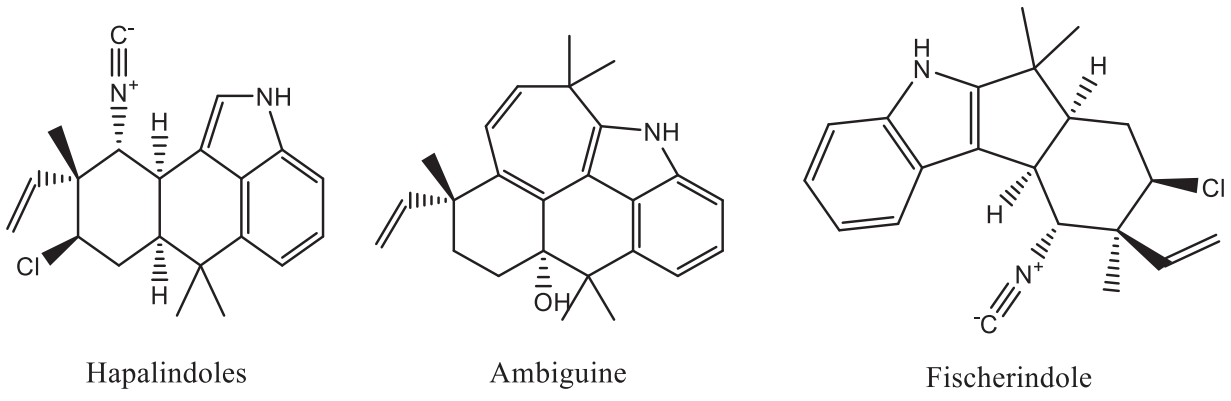


Fig. 4. Chemical structures of alkaloids from cyanobacteria.

have been carried out to assess these metabolic changes in microalgae, in order to understand their nature and discover useful compounds for humans [102]. These compounds include fatty acids, Proteins, pigments, and vitamins of microalgal origin, produced in response to environmental variations. These substances possess antibacterial, antiviral, anti-algae, anti-enzymatic, and antifungal properties [102] (Table 2).

3.1. Terpenoids

The photosynthetic nature of microalgae highlights their remarkable efficiency as a source of terpenoids (Table 2). For the industrial production of astaxanthin and *β*-carotene, respectively, artificial cultures of *Haematococcus pluvialis* and *Dunaliella salina* were created [103]. Other microalgae species also produce various terpenoids, such as xanthophyll, antaxanthin, canthaxanthin, squalene (*E*)-alpha-bisabolene, patchoulol, manoyl oxide, and lupeol (Fig. 5, Table 2). Certain microalgae are particularly considered as promising cellular sources for the production of terpenoids, including *Aurantiochytrium* sp. [104], *Schizochytrium* sp. [105], *Thraustochytrids* sp. [106–108], *Schizochytrium limacinum* [109], *Schizochytrium mangrovei* [110,111], *Aurantiochytrium* sp. [112,113], *Chlamydomonas reinhardtii* [92,114,115], and *P. tricornutum* [116].

Table 2
Bioactive compounds produced by microalgae species.

Compounds	Microalgae species	References
Terpenoid		
β-Carotene	*D. salina* and *Thraustochytrids* spp.	[106,108]
Xanthophyll	*Aurantiochytrium* sp.	[104]
Cantaxanthin	*Schizochytrium* sp. and *Thraustochytrids* spp.	[105,106]
Astaxanthin	*Haematococcus pluvialis, Schizochytrium* sp., *S. limacinum, Aurantiochytrium* sp., and *Thraustochytrids* spp.	[103,105-107, 109,111,112]
Squalene	*S. mangrovei,* and *Aurantiochytrium* sp.	[110,140] [113,141]
(*E*)-α-Bisabolene	*Chlamydomonas reinhardtii*	[114]
Patchoulol		[115]
Manoyl oxide		[92]
Lupeol	*Phaeodactylum tricornutum*	[116]
Phenolic acids		
Gallic acid, *trans*-cinnamic acid, caffeic acid, synapic acid, chlorogenic acid, and quinic acid	*Chlorella* sp.	[126]
Flavonoids		
Myricetin	*Dunaliella tertiolecta*	[127]
Luteolin-7-glucoside	*Diacronema lutheri*	[126]
Kaempferol	*Nannochloropsis* sp.	[71]
Dimethoxyflavon	*Tetraselmis suecica*	[71]
Vitamins		
Provitamin A	*Porphyridium cruentum*	[129]
Vitamin E (α-tocopherol),	*Tetraselmis suecica*	[129]
Vitamin C	*Tetraselmis suecica*	[129]
Polysaccharides		
Rhamnan sulfate	*Cochlodinium polykrikoides*	[132]
Laminarin	*Laminaria digitata*	[133,134]
Ulvan	*Ulva* sp.	[135]
Other compounds		
Cholesterol	*Chaetoceros* sp., *Porphyridium* sp., and *Nannochloropsis* sp.	[136–138]
Stigmasterol β-Sitosterol	*Isochrysis* sp.	[139]

The synthesis of terpenoids has it origin in the isoprene unit (C_5H_8) composed of 5 carbons, present in the isomeric compounds dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) that form the fundamental building unit of terpenoids. Gradual addition of DMAPP to IPP units induces the production of longer chain terpenoids that maintain the isoprene rule [117]. Terpenes are divided into different classes, ranging from hemiterpenoids (C5) to polyterpenes (> C40), including monoterpenoids (C10), diterpenoids (C20), sesquiterpenoids (C15), tetraterpenoids (C40), and triterpenoids (C30). The 2-C-methyl-d-erythritol-4-phosphate (MEP) and mevalonate (MVA) pathways, known as the DXP pathways, play a role in creating isoprenoid precursors DMAPP and IPP [118].

For the synthesis of terpenoids, plants use two mechanisms, namely MEP, which is active in endotoxin, whereas MVA is used in the cytosol. Archaebacteria, eukaryotes, and some bacteria separately use the MEP and the MVA pathways in their cytosol. Both processes require seven oxidative steps to produce DMAPP and IPP, but their starting materials are different. Indeed, MVA and MEP start from the precursor molecules; pyruvate and GAP, respectively [119]. The condensation of GAP with DXP is the initial step in the MEP pathway, an irreversible process. This step is driven by an essential enzyme called DXP synthase (DXS). DXP then undergoes a reductive rearrangement to form 4-(cytidine 5′-pyrophospho)-2-C-methyl-derythritol (CDP-ME). Once this chemical compound is formed, it is then phosphorylated, cyclized, and dehydrated by reduction resulting in the formation of 4-hydroxy-3-methylbutenyl 1-diphosphate (HMB-PP). Hence, the enzyme HMB-PP reductase interacts with HMB-PP to produce either IPP or DMAPP, a process catalyzed by the enzyme IspH [120].

The MEP pathway does not maintain a regular ratio between IPP and DMAPP in the presence of IDI enzyme, responsible for the interconversion of DMAPP and IPP. The process begins with the joining of two molecules of acetyl-CoAs, forming acetoacetyl-CoA that is then condensed with a third acetyl-CoA molecule to form 4-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) [120]. Eventually, the decrease of HMG-CoA creates MVA, which is then phosphorylated twice to create mevalonate pyrophosphate. The third phase of decarboxylation and phosphorylation leads to the formation of IPP. IPP is interconverted to DMAPP by the enzyme IDI [120].

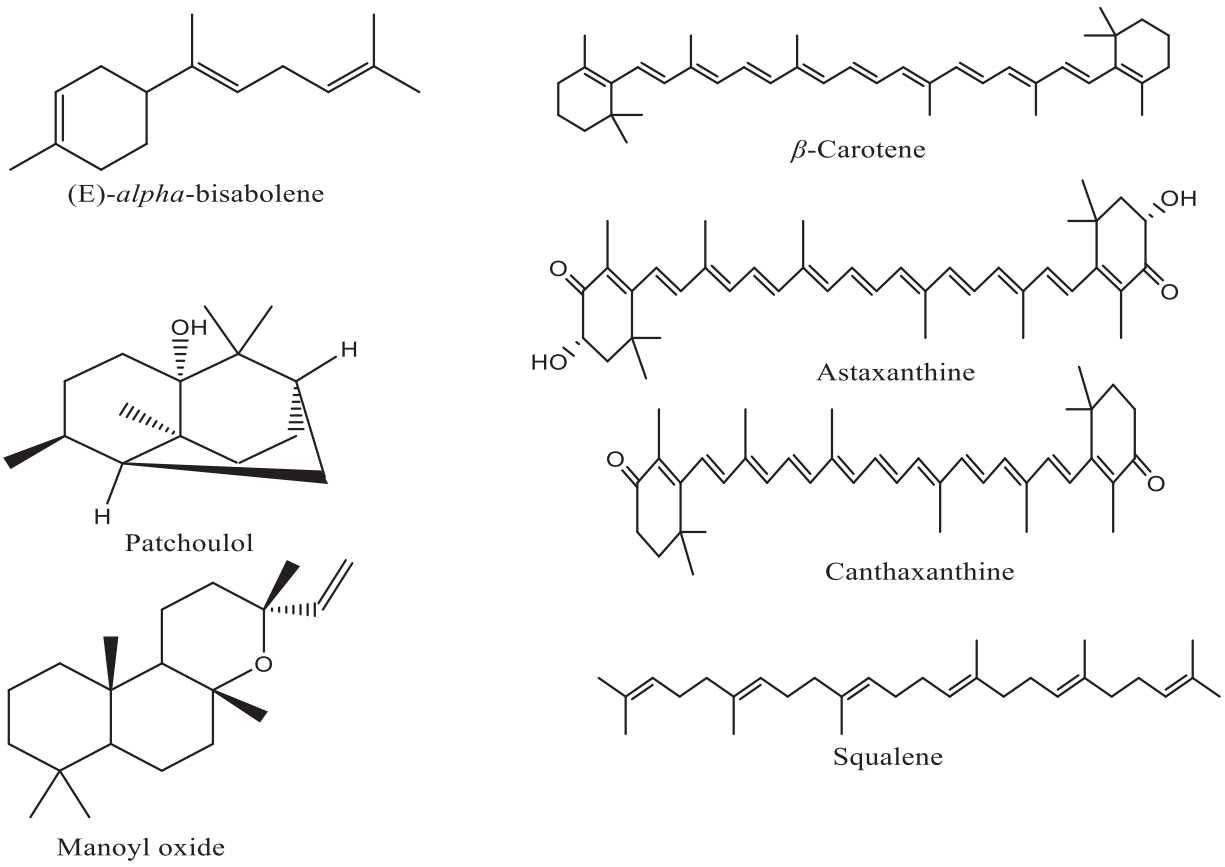


Fig. 5. Chemical structures of terpenoids from microalgae.

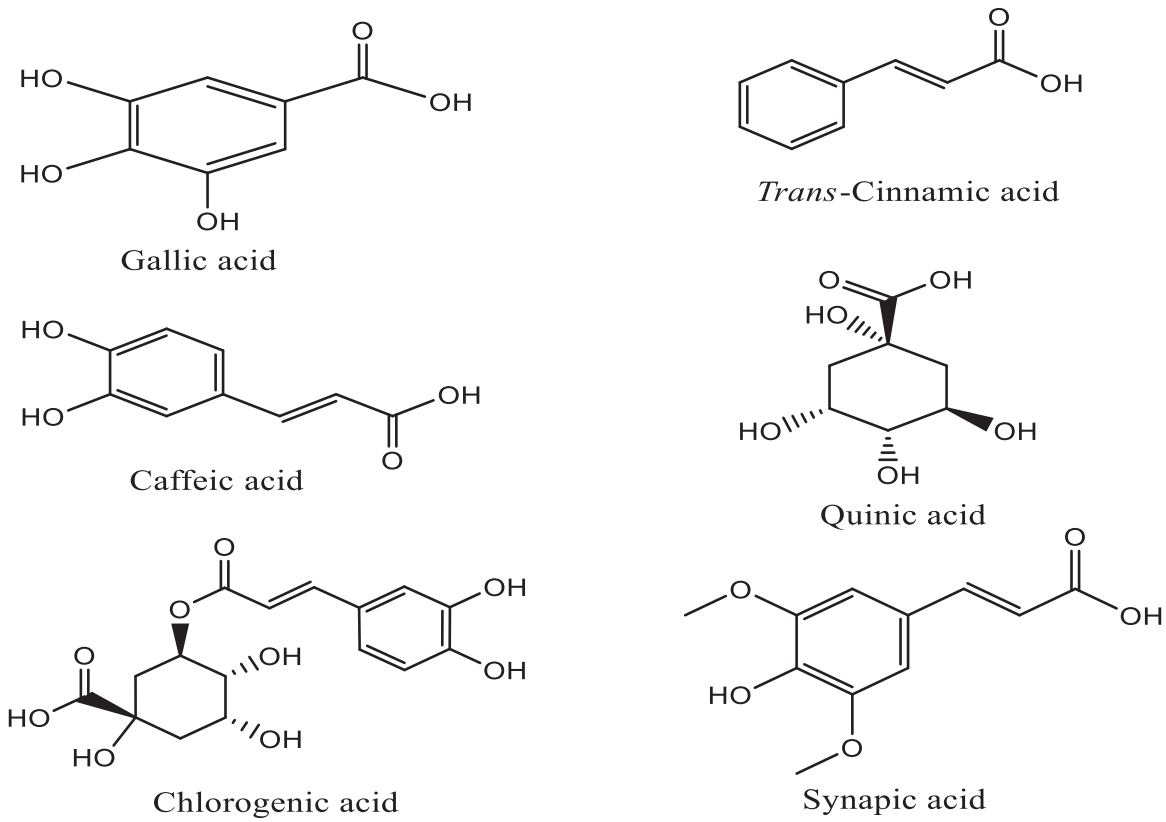


Fig. 6. Chemical structures of phenolic acids from microalgae.

Regardless of the pathway that generates DMAPP and IPP, all organisms follow the same subsequent process. These two molecules are successively condensed head-to-tail to give rise to a range of prenyl phosphates of varying lengths, such as C20 geranylgeranyl pyrophosphate (GGPP), C15 farnesyl pyrophosphate (FPP), and C10 geranyl pyrophosphate (GPP). These prenyl phosphates, in turn, serve as precursors for the synthesis of multiple tetraterpenes through the effect of terpene synthase (TPS) [121,122].

The MEP pathway is typically applied for bioengineering cyanobacteria for many reasons. First, this pathway is more tightly regulated because it matches the natural pathway [123]. Second, integrating 7 genes, each larger than 1.5 kb, into the system is difficult since the MVA method is not of cyanobacterial origin [124]. Additionally, successful MVA pathway expression yields similar results to MEP method building [93]. Third, compared to the MVA pathway, which uses approximately 56 % organic matter (carbon), the MEP pathway is more "energy-deficient" but converts carbon sources more efficiently (83 %) to produce the IPP precursor [125].

3.2. Phenolic acids

Phenolic acids are another class of phytochemicals found in microalgae [126]. *Tetraselmis chlorella* is characterized by its richness in trans-cinnamic acid, chlorogenic acid, synapic acid, gallic acid, quinic acid, and caffeic acid (Fig. 6, Table 2).

3.3. Flavonoids

Goiris et al. [126] demonstrated that microalgae are rich in flavonoids [126]. Flavonols such as myricetin have been isolated from *Dunaliella tertiolecta*, while kaempferol has been found in Nannochloropsis sp., [71,127]. As for flavones, luteolin-7-glucoside is produced by *Diacronema lutheri*, and dimethoxyflavone by *Tetraselmis suecica* [71,126] (Fig. 7; Table 2).

3.4. Vitamins

Microalgae are recognized as promising producers of vitamins, offering the potential to reduce oxidative damage and related conditions. Numerous trials were performed to test the antioxidant properties of vitamins C and E. Their effects have also been tested on smokers in order to evaluate their chemopreventive activity [128]. Fabregas and Herrero [129] showed that *T. suecica* is an important producer of vitamin C, as well as vitamin E (α-tocopherol), while *Porphyridium cruentum* synthesizes provitamin A (Table 2).

3.5. Polysaccharides

Polysaccharides from microalgae and marine organisms [130] contribute to their antioxidant properties, which are inversely correlated to their sulfate levels [131] (Table 2). Rhamnan sulfate is produced by *Cochlodinium polykrikoides* [132], laminarin is produced by the brown algae *Laminaria digitata* [133,134], while ulvan is produced by *Ulva* sp., which can act as a plant defense elicitor [135].

3.6. Others

Microalgae also represent a rich source of sterols, including cholesterol produced by *Chaetoceros, Porphyridium,* and *Nannochloropsis* strains [136–138]. Moreover, stigmasterol and β-sitosterol are produced by *Isochrysis* strains [139] (Table 2).

4. Anticancer properties of cyanobacteria and microalgae extracts

Cyanobacteria and microalgae produce various bioactive compounds with anti-proliferative and cell death against several human tumor cells (Fig. 8). Paul et al. [142] tested the antiproliferative potential of two cyanobacterial taxa, *Phormidium tenue* and *Phormidium valderianum*, on cervical cancer (HeLa) cells. Therefore, the tested extracts reduced cell

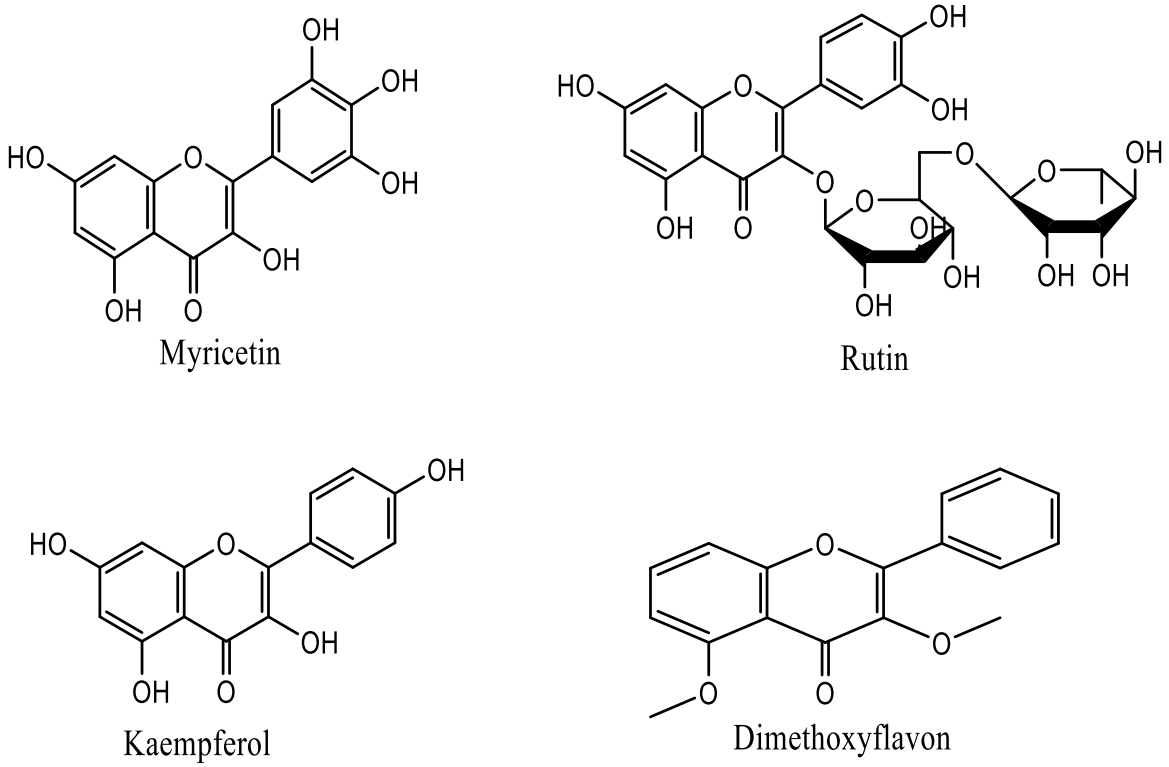


Fig. 7. Microalgae flavonoids' chemical compositions.

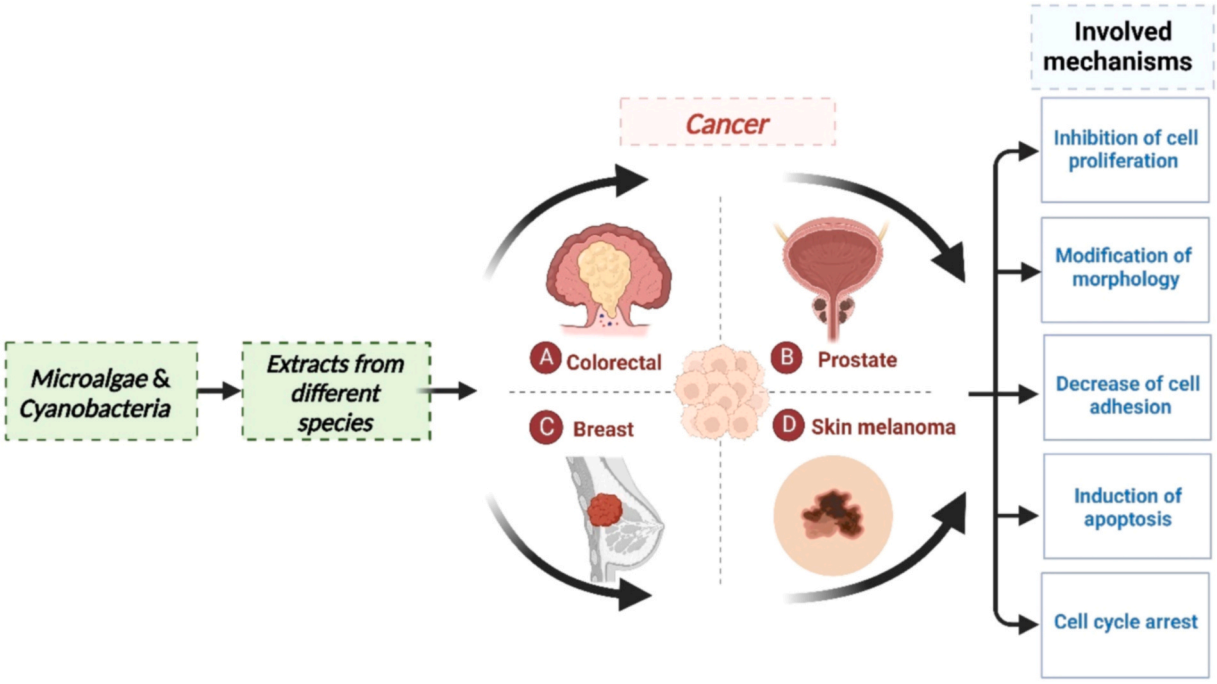


Fig. 8. Anticancer potential of extracts from microalgae and cyanobacteria on various types of human cancers.

viability in a concentration-dependent manner, with 11.46 % and 19.33 % inhibition, respectively.

The extract of *Lyngbya aestuarii* cyanobacteria reduced cell viability for different cancer cell lines by 62.78 ± 2.13 % for HepG2, 61.38 ± 3.26 % for HT-29, 76.93 ± 12.98 % for T47D, and 69.68 ± 4.89 % for MG-63 [143]. In addition, Mukund et al. [144] assessed the anti-proliferative potential of the *Oscillatoria terebriformis* cyanobacteria extract on lung cancer cells. Consequently, the extract of *O. terebriformis* had marked anticancer action on A549 cells (IC_{50} = 14.67 ± 0.98 μg/mL) causing cell morphological alterations and inducing apoptosis. Furthermore, the extract of *O. terebriformis* significantly reduced MCF-7 cell viability by increasing the expression of the caspase-9 gene.

In a study performed by Wali et al. [145], the effects of the extract from *Nannochloropsis oculata* microalga on the MDA-MB-231 cell were analyzed. A decrease in cell viability was recorded, accompanied by morphological changes in the cells. Using various in vitro assays, Tavares-Carreón et al. [146] recorded that the methanolic extract of the microalgae *Granulocystopsis* sp. exhibited potent anticancer activity with an IC_{50} of 13.74 ± 2.06 mg/mL, 16.70 ± 3.09 mg/mL, 17.20 ± 2.16 mg/mL, and 17.44 ± 1.64 mg/mL, against prostate, breast, cervical, and skin melanoma cell lines, respectively. The extracts studied targeted multiple checkpoints, including inhibiting cell proliferation, altering morphology, reducing cell adhesion, and inducing apoptosis *via* caspase-3/7 pathway activation. In another study conducted by Reyna-Martinez et al. [147], methanolic extracts of *Scenedesmus* sp. and *Chlorella sorokiniana*, two types of microalgae, demonstrated significant cancer cell toxicity. At 500 μg/mL, they induced toxicity of 61.89 ± 3.26 % and 74.77 ± 1.84 %, respectively, in a murine lymphoma cell line L5178Y-R, with $IC5_0$ values of 460.0 ± 21.5 and 362.9 ± 13.5 μg/mL, by activating cell death. Moreover, the DMSO extract of *Chlorella* sp., another microalgae, also showed significant toxicity against a B16F10 murine melanoma cell line at a dose of only 2 μg/mL, reducing cell viability by up to 56 % (IC_{50} = 5.5 μg/mL) [148].

Furthermore, Suh et al. [149] demonstrated the properties of an ethanolic extract of an Antarctic freshwater microalgae, *Micratinium* sp., which reduced the proliferation of HCT116 cell lines by blocking the cell cycle in the G_1 phase. This action was achieved through the modulation of G_1/S regulator expression levels. In contrast, Alateyah et al. [150] performed an experience on the anticancer effect of the methanol crude extract of *Haematococcus pluvialis* green microalgae against MDA-MB-231 cells. Consequently, *H. pluvialis* significantly decreased cell growth of breast cancer by down-regulating invasive cancer cells and inducing cell death by p53/Bax/Bcl2 pathway activation. The cytotoxicity of algal extracts was also confirmed by several studies. Shanab et al. [151] reported that an aqueous extract of the green alga strain *Chlorella vulgaris* showed remarkable anticancer efficacy, with high rates of 89.4 % and 87.25 % inhibition on hepatocarcinoma and Ehrlich's ascites carcinoma (EAC) cells, respectively. Similarly, Somasekharan et al. [152] examined the impact of an aqueous preparation of Canadian marine microalgae on prostate, lung, breast, stomach, and pancreatic cancer cell lines. This microalga exhibited antimetastatic activity on cancer cells by downregulating the colony-forming ability (CFA) as well as the preferential destruction of CTCs/CTMs. Furthermore, the antiproliferative activity of the extract of red microalgae, *Rhodosorus marinus*, was also tested by Garcia-Galaz et al. [153] against numerous cancer cell lines, using the spectrophotometric technique MTT method. The results demonstrated significant anticancer effects, with IC_{50} values of 0.5 mg/mL for colon, 0.8 mg/mL for cervical, 0.9 mg/mL for breast, 0.4 mg/mL for prostate, and 0.1 mg/mL for breast cancer cells.

The in vivo anticancer effect of *Euglena tuba* methanol extract against Dalton's lymphoma cells was investigated using MTT and Western blot analysis. The treatment with *E. tuba* extract showed significant cytotoxicity by supressing mitochondrial potential, activating proapoptotic (p53, Cyt-c, and Bax) proteins, and inhibiting anti-apoptotic (Bcl2) protein [154]. In contrast, methanol extract of *Desmococcus olivaceus* microalgae and the acetone extract of *Chlorococcum humicola* demonstrated potent selective inhibition of laryngeal cancer cell growth, with IC_{50} values of 1.56 and 0.625 μg/mL, respectively [155]. In a study performed by Arslan et al. [156], the antitumor potential of *Isochrysis galbana* extract was evaluated on the cancer cell lines U937, MOLT-4, HL60, Raji, and K562. According to the experimental results, this microalga exhibited cytotoxicity of less than 50 % in all cells, with IC_{50} greater than 500 μg/mL.

5. Anticancer potential of bioactive compounds from cyanobacteria and microalgae

Recent investigations on marine species led to the determination of many prospective molecules from sea slugs, sea sponges, nemertine worms, snails, bryozoans, and ascidians. Among these marine organisms, algae and cyanobacteria produce an array of valuable natural products, especially anticancer agents.

5.1. In vitro investigations and mechanisms of action

5.1.1. Anticancer potential of bioactive compounds from cyanobacteria

Many compounds isolated from cyanobacteria exhibited promising anticancer properties. Among these compounds are lactones, pigments, fatty acid amines, peptides, linear peptides, ketopeptides, macrocyclic depsipeptides, cyclic depsipeptide, and lipopeptides (Table 3). These various classes of compounds represent a rich and varied source of potentially beneficial molecules in the fight against cancer.

5.1.1.1. Lactones

5.1.1.1.1. Tolytoxin. Tolytoxin, a macrolide obtained from freeze-dried cells of *Scytonema ocellaturn*, showed to be an effective cell growth inhibitor in different mammalian cells [157]. The macrolide scytophycin A-E, extracted from *Scytonema pseudohofmanni*, demonstrated cytotoxic activity on nasopharyngeal cancer (kB) cells, with an IC_{50} greater than 5 ng/mL [158].

5.1.1.1.2. Caylobolide. Caylobolide A, a macrolactone derived from *L. majuscula*, demonstrated in vitro cytotoxic effect against human colon tumor HCT-116 cells [159]. Caylobolide B, obtained from *Phormidium* sp., presented a strong cytotoxic effect on cervical carcinoma HeLa cells (IC_{50} = 12.25 μM) and colorectal tumor HT-29 cells (IC_{50} = 4.5 μM) [160].

5.1.1.2. Pigments. In order to search for an alternative approach to treat chronic inflammatory diseases that are related to the development of different types of cancers, Stevenson et al. [161] investigated the potential role of scytonemin, derived from the extracellular sheath of *Stigonema* sp., in inhibiting key kinases involved in hyperproliferative inflammatory diseases. Their findings revealed that this natural product has an antiproliferative effect on Jurkat T cells by promoting apoptosis [161]. Scytonemin prevented mitotic spindle formation by inhibiting polo-like kinase 1 (PLK1, an enzyme crucial for the G_2-M transition) and by blocking the activity of serine/threonine kinases [161]. In a work by Evans et al. [162], the potential of scytonemin was evaluated on melanoma cells at doses of 2 and 10 μM. Therefore, this molecule significantly inhibited melanoma cell proliferation (IC_{50} value of 1.66 ± 0.34 μM). This inhibition occurred in a dose-dependent manner by targeting key cell cycle enzymes involved in tumor development. Furthermore, scytonemin has also been observed to promote spleen cell proliferation, suggesting its potential application to stimulate immune reactivity [162]. In their investigation, Zhang [163] found that scytonemin suppressed the growth and arrested the cycle of myeloma cells by directly reducing Plk1 protein effect. Scytonemin could be considered as a potent novel agent for the management of multiple myeloma [163].

5.1.1.3. Fatty acid amines

5.1.1.3.1. Isomalyngamide. Chang T. T. et al. [164] reported that isomalyngamide A and isomalyngamide A-1, isolated from *L. majuscula*, showed promising therapeutic properties against breast cancer MCF-7 (isomalyngamide A: IC_{50} = 4.6 μM; isomalyngamide A-1: IC_{50} = 12.7 μM) as well as on MDA-MB-231 cells (isomalyngamide A: IC_{50} = 2.8 μM; isomalyngamide A-1: IC_{50} > 20 μM). These compounds acted by blocking the expression of phosphorylated focal adhesion protein kinase (p-FAK), Akt, FAK, and p-Akt, by the integrin β1-mediated pathway, thereby exhibiting an anti-metastatic effect.

Table 3
In vitro investigations and mechanisms of action of extracts and bioactive components extracted from cyanobacteria.

Secondary metabolite (source)	Investigated cell lines	Key results	References
Macrocyclic lactone			
Tolytoxin 6-Hydroxyscytophycin B (*Seytonema ocellaturn*) 19-O-Demethylscytophycin C 6-Hydroxy-7-O-methylscytophycin E	L1210 (murine leukemia), LoVo (human adenocarcinoma), KB (human epidermoid carcinoma), Hep-2 (human epithelial type 2 cells), HBL-100 (breast cancer cell), HL-60 (promyelocytic leukemia), COLO-201 (colon adenocarcinoma), T47-D (ductal carcinoma), KATO-III (gastric carcinoma)	L1210: IC_{50} = 3.9 nM; LoVo: IC_{50} = 8.4 nM KB: IC_{50} = 5.3 nM; HEp-2: IC_{50} = 2.3 nM HL-60: IC_{50} = 4.8 nM; HBL-100: IC_{50} = 2.4 nM T47-D: IC_{50} = 4.9 nM; COLO-201: IC_{50} = 0.52 nM KATO-III: IC_{50} = 0.78 nM Exhibited anticancer activity Inhibited growth Increased cytotoxicity	[157]
Scytophycin A–E (*Scytonema pseudohofmanni*)	KB and LoVo cells	IC_{50} > 5 ng/mL Exhibited anticancer activity Increased cytotoxicity	[158]
Macrolactone			
Caylobolide A (*Lyngbya majuscula)*	HCT-116 colon tumor	IC_{50} = 9.9 μM Exhibited anticancer activity Increased cytotoxicity	[159]
Caylobolide B (*Phormidium* sp.)	HT29 colorectal cancer cells HeLa cervical cancer cells	HT29: IC_{50} = 4.5 μM; HeLa: IC_{50} = 12.2 μM Exhibited anticancer activity Increased cytotoxicity	[160]
Pigment			
Scytonemin (*Stigonema* sp.)	Cancerous Jurkat T cell line	IC_{50} = 7.8 μM Suppressed mitotic spindle formation Inhibited apoptosis and protein serine/threonine kinase activity	[161]
	B16-F1 melanoma cells	IC_{50} = 1.66 ± 0.34 μM Exhibited anti-proliferative potential Inhibited cell growth	[162]
	Multiple myeloma cells	Inhibited cell proliferation Arrested cell cycle Down-regulated PLK1 activity	[163]
Fatty acid amines			
Isomalyngamide A and isomalyngamide A-1 *(L. majuscula)*	MCF-7 and MDA-MB-231 cells	Isomalyngamide A: MCF-7: IC_{50} = 4.6 μM; MDA-	[164]

(*continued on next page*)

Table 3 (*continued*)

Secondary metabolite (source)	Investigated cell lines	Key results	References
		MB-231: IC_{50} = 2.8 μM Isomalyngamide A-1: MCF-7: IC_{50} = 12.7 μM; MDA-MB-231: IC_{50} > 20 μM Inhibited cell proliferation, apoptosis and cell migration Inactivated the expression of p-FAK/FAK/p-Akt/Akt through β1-integrin signaling Induced antimetastatic potency	
Jamaicamides A, B, and C (*L. majuscula*)	H-460 lung cancer and neuro blastoma cell lines	LC_{50} approximatively 15 μM for all Inhibited cell proliferation Exhibited cytotoxicity	[165]
Macrocyclic depsipeptide			
Grassypeptolide A, B and C (*L. confervoides*)	Human osteosarcoma (U2OS), HeLa, HT29, and neuroblastoma (IMR-32)	Grassypeptolide: IC_{50}: 1–4.2 μM for in all cell lines Grassypeptolide A: HT29: IC_{50} = 1.22 μM; Hela: IC_{50} = 1.01 μM Grassypeptolide B: HT29: IC_{50} = 4.07 μM; Hela: IC_{50} = 2.93 μM Grassypeptolide C: HT29: IC_{50} = 76.7 μM; Hela: IC_{50} = 44.6 μM Inhibited cell proliferation Induced G_1 or G_2/M cell cycle arrest	[166,167]
Linear peptide			
Tasiamide B (*Symploca* sp.)	KB and LoVo cells	Kb cells: IC_{50} = 0.48 μg/mL Lovo cells: IC_{50} = 3.47 μg/mL Inhibited cell proliferation Increased cytotoxicity	[168],
Tasiamide B derivatives B-9	MDA-MB-231 cell lines	Induced highly potent inhibition towards cathepsin D	[169]
Ketopeptide			
Curacin A (*L. majuscula*)	A549 cells	IC_{50} = 0.72 ± 0.02 μM Inhibited cell proliferation Induced apoptosis Induced G_2/M cell cycle arrest Inhibited tubulin polymerization	[173,175]
Cyclic depsipeptide			
Apratoxin A (*L. majuscula*)	U2OS, HeLa, KB, and LoVo cells	U2OS: IC_{50} = 50 nM; HeLa: IC_{50} = 2.2 nM KB: IC_{50} = 0.36 nM; LoVo: IC_{50} = 0.52 nM Inhibited cell cycle at G1 Phase and secretory pathway Induced cytotoxicity Inhibited translocation of protein targeting Sec61α	[178,179]
Apratoxin B (*Lyngbya* sp.)	KB and LoVo cells	KB: IC_{50} = 21.3 nM; LoVo: IC_{50} = 10.8 nM Induced cytotoxicity	[179]
Apratoxin C (*Symploca* sp.)	Several tumor cells	Induced cytotoxicity	
Apratoxin D (*L. majuscula* and *L. sordida)*	H-460 cells	IC_{50} = 2.6 nM Induced cytotoxicity	[178]
Apratoxin E (*Lyngbya bouilloni*)	U2OS, HT29, and HeLa cells	U2OS: IC_{50} = 59 nM; HT29: IC_{50} = 21 nM HeLa: IC_{50} = 72 nM Increased antiproliferative effect	[180]
Apratoxin F (*Lyngbya* sp.)	H-460 and HCT-116 colorectal cancer cells	H-460: IC_{50} = 2 nM; HCT-116: IC_{50} = 36.7 nM Induced cytotoxicity	[181]
Apratoxin G (*Lyngbya* sp.)	H-460 and HCT-116 cells	H-460: IC_{50} = 14 nM HCT-116: IC_{50}: not determined Induced cytotoxicity	
Coibamade A (*Leptolyngbya* sp.)	U87-MG and SF-295 glioblastoma cells	IC_{50} = 20 nM Induced cytotoxicity Suppressed tumor growth	[183]
	Normal human umbilical vein endothelial cells (HUVECs)	Inhibited proliferation Down-regulated VEGFA/VEGFR2 expression	
	Melanoma LOX IMVI, HL-60, astrocytoma SNB75, and MDA-MB-231	MDA-MB-231: IC_{50} = 2.8 nM; LOX IMVI: IC_{50} = 7.4 nM; HL-60: IC_{50} = 7.4 nM; SNB75: IC_{50} = 7.6 nM Exhibited potent antiproliferative effect Induced cytotoxicity Induced G_1 cell cycle arrest	[45]
	U87-MG glioblastoma cells and SF-295 glioblastoma cells	U87-MG: IC_{50} = 28.8 nM; SF-295: IC_{50} = 96.2 nM Induced	[184]

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Table 3 (*continued*)

Secondary metabolite (source)	Investigated cell lines	Key results	References
		cytotoxicity, cell death, and mTOR-independent autophagy	
Lyngbyabellin A (*L. majuscula*)	KB and LoVo cells	KB: IC_{50} = 0.03 μg/mL; Lovo: IC_{50} = 0.05 μg/mL Increased cytotoxicity Inhibited tumor cell cycle arrest at G_2/M phase Enhanced actin polymerization	[185]
Lyngbyabellin B (*L. majuscula*)		KB: IC_{50} = 0.10 μg/mL; Lovo: IC_{50} = 0.83 μg/mL Increased cytotoxicity Inhibited tumor cell cycle arrest at G_2/M Phase Enhanced actin polymerization	
Lyngbyabellin E (*L. majuscula*)	NCI-H460 and neuroblastoma cell lines	NCI-H460: IC_{50} = 0.4 μM; neuro-2a: IC_{50} = 1.2 μM Inhibited tumor growth and cell microfibrils network	[186]
Lyngbyabellin F (*L. majuscula*)		NCI-H460: IC_{50} = 1 μM; neuro-2a: IC_{50} = 1.8 μM Increased cytotoxicity	
Lyngbyabellin G (*L. majuscula*)		NCI-H460: IC_{50} = 2.2 μM; neuro-2a: IC_{50} = 4.8 μM Increased cytotoxicity	
Lyngbyabellin H (*L. majuscula*)		NCI-H460: IC_{50} = 0.2 μM; neuro-2a: IC_{50} = 1.4 μM Increased cytotoxicity	
Lyngbyabellin I (*L. majuscula*)		NCI-H460: IC_{50} = 1 μM; neuro-2a: IC_{50} = 0.7 μM Increased cytotoxicity	
Lyngbyabellin N (*M. bouillonii*)	HCT116 colon tumor cell	IC_{50} = 40.9 ± 3.3 nM Exhibited anticancer activity Increased cytotoxicity	[187]
Cryptophycin (*Nostoc* sp.)	L1210 murine leukemia cells	Inhibited microtubule assembly Induced cell cycle arrest in G_2/M phase and apoptosis	[51][190]
	LoVo and KB cells	KB: IC_{50} = 4.58 pM; Lovo: IC_{50} = 7.63 pM Induced apoptosis	[191]
	MDA-MB-435 and SKOV3 cell lines	IC_{50} = 50 pM Inhibited	[44,213]

Table 3 (*continued*)

Secondary metabolite (source)	Investigated cell lines	Key results	References
		proliferation and cell cycle at G_2/M phase	
Lagunamides A, B (*L. majuscula*)	P388 leukemia cell line	IC_{50}: 6.4–20.5 nM Increased cytotoxicity	[188]
Lagunamide C (*L. majuscula*)	A549, P388, HCT8, PC3, and SK-OV3 carcinoma cell lines	IC_{50}: 2.1–24.4 nM	[188]
Hoiamide A (*L. majuscula*)	H-460 lung neuroblastoma cell lines H-460 lung neuroblastoma cell lines	H-460: IC_{50} = 11.2 μM; neuro-2a: IC_{50} = 2.1 μM Enhanced cytotoxicity and neurotoxicity	[193]
Hoiamide B (*P. gracile*)		H-460: IC_{50} = 8.3 μM; neuro-2a: IC_{50} = no effect Enhanced cytotoxicity and neurotoxicity	
Homodolastatin 16 (*L. majuscula*)	WHCO1 and WHCO6 esophageal cancer cell lines ME180 cervical tumor cell line	WHCO1: IC_{50} = 4.3 μg/mL; WHCO6: IC_{50} = 10.1 μg/mL; ME180: IC_{50} = 8.3 μg/mL Induced both apoptosis, cytotoxicity as well as arrested cell cycle at G_2/M phase	[194]
Largazole (*Symploca* sp.)	MDA-MB-23I, U2OS, and HT29 cells Neuroblastoma IMR-32 Nontransformed murine mammary epithelial cells NMuMG HCT-116 colorectal carcinoma	MDA-MB-23I: IC_{50} = 7.7 nM; U2OS: IC_{50} = 55 nM HT29: IC_{50} = 12 nM; IMR-32: IC_{50} = 16 nM NMuMG: IC_{50} = 122 nM; HCT-116: IC_{50} = Not specified Increased cytotoxicity Inhibited tumor proliferation Arrested cell cycle at G_2/M phase Inhibited HDAC	[58,195]
Majusculamide C (*L. majuscula*)	OVCAR-3, lung cancer NCI-H460 colorectal cancer KM20L2, kidney cancer A498, and glioblastoma SF-295	OVCAR-3: IC_{50} = 0.51 μg/mL; A498: IC_{50} = 0.058 μg/mL; NCI-H460: IC_{50} = 0.0032 μg/mL; KM20L2: IC_{50} = 0.0013 μg/mL; SF-295: IC_{50} = 0.013 μg/mL Showed anticancer action Induced cytotoxicity	[185,196]
Obyanamide (*L. confervoides*)	KB and LoVo cells	KB cells: IC_{50} = 0.58 μg/mL; LoVo cells: IC_{50} = 3.14 μg/mL Exhibited	[197]

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Table 3 (*continued*)

Secondary metabolite (source)	Investigated cell lines	Key results	References
		anticancer activity	
Palau'amide (*L. confervoides*)	KB cells	IC_{50} = 13 nM Exhibited anticancer activity	[198]
Palmyramide A (*L. majuscula*)	Neuro2a cells Human lung cell H-460	Neuro2a: IC_{50} = 17.2 μM; H-460: IC_{50} = 39.7 μM Showed anticancer effect Induced cytotoxicity Blocked the voltage regulated sodium channel	[199]
Pitipeptolide A (*L. majuscula*)	HT29 colon adenocarcinoma cancer cells LoVo and MCF-7 cells	HT29: IC_{50} = 13 μM; MCF-7: IC_{50} = 13 μM Lovo: IC_{50} = 2.25 μM Showed anticancer action Induced cytotoxicity	[21,200]
Pitipeptolide B (*L. majuscula*)	HT29, LoVo, and MCF-7 cells	HT29: IC_{50} = 13 μM; MCF-7: IC_{50} = 11 μM Lovo: IC_{50} = 1.95 μM Showed anticancer action Induced cytotoxicity	[21,200]
Pitiprolamide (*L. majuscula*)	HCT116 and MCF7 cells	HCT116: IC_{50} = 33 μM; MCF7: IC_{50} = 33 μM Showed anticancer action Induced cytotoxicity	[200]
Tasipeptins A (*Symploca* sp.)	KB cells	KB: IC_{50} = 0.93 μM Showed anticancer action Induced cytotoxicity	[202]
Tasipeptins B (*Symploca* sp.)	KB cells	KB: IC_{50} = 0.82 μM Showed anticancer action Induced cytotoxicity	
Ulongapeptin (*Lyngbya* sp.)	KB cells	KB: IC_{50} = 0.63 μM Showed anticancer action Induced cytotoxicity	[203]
Peptide			
Bisebromoamide (*Lyngbya sp.*)	HeLa S3 cells A panel of 39 tumor cells of the Japanese Foundation for Cancer Research (JFCR39)	HeLa S3: IC_{50} = 0.04 μg/mL; JFCR39: IC_{50} = 40 nM Enhanced cytotoxicity Inhibited protein kinases and phosphorylation of ERK	[204,205]
Lipopepetides			
Dragonamide/Pseudo-dysidenin (*L. majuscula*)	P-388, A-549, adenocarcinoma,	IC_{50} > 1 μg/mL Showed	[206]

Table 3 (*continued*)

Secondary metabolite (source)	Investigated cell lines	Key results	References
	HT-29, and MEL-28 cells	anticancer action Induced cytotoxicity	
Somocystinamide A (*L. majuscula*)	Jurkat (T cell leukemia), CEM (leukemia), A549 cells Molt4 (T cell leukemia), M21 melanoma, and U266 myeloma cells	Jurkat: IC_{50} = 3 nM; CEM: IC_{50} = 14 nM A549: IC_{50} = 46 nM; Molt4: IC_{50} = 60 nM M21: IC_{50} = 1.3 μM; U266: IC_{50} = 5.8 μM Increased cytotoxicity Induced apoptosis *via* caspase 8	[207]
Kalkitoxin (*Phormidium* sp.)	HCT-116 and T47D cells	HCT-116: IC_{50} = 2.7 nM; T47D: IC_{50} = 5.6 nM Exhibited anticancer potential Induced cytotoxicity Inhibited hypoxia-induced activation of HIF-1 Decreased mitochondrial oxygen consumption Blocked VEGF	[208]

5.1.1.3.2. Jamaicamides. Jamaicamides C, B, and A, extracted from a strain of *L. majuscula*, a dark green cyanobacterium, demonstrated significant cytotoxicity on mouse neuroblastoma and human lung cells. LC_{50} values for all three compounds (C, B, and A) were 15 μM for both cell lines, thus highlighting their promising potential as cytotoxic agents against these cell types [165].

5.1.1.4. Macrocyclic depsipeptide. The macrocyclic depsipeptide grassypeptolide and its derivatives, grassypeptolides C, B, and A containing bis-thiazoline from *Lyngbya confervoides* (marine cyanobacterium), have demonstrated antiproliferative cytotoxic action against a variety of cancers, namely cervical carcinoma (HeLa), human osteosarcoma (U2OS), neuroblastoma (IMR-32), and colorectal adenocarcinoma (HT-29) cell lines [166]. More specifically, grassypeptolides A, B and C markedly suppressed the proliferation of colorectal adenocarcinoma HT-29 cells, with IC_{50} of 1.22, 4.07, and 76.7 μM, respectively. Similarly, they also exhibited marked inhibition of cervical carcinoma (HeLa) cell proliferation, with IC_{50} values of 1.01, 2.93, and 44.6 μM, respectively. This inhibition has been observed in a dose-dependent way, namely the cell cycle arrest during the G_2/M or G_1 phases [167].

5.1.1.5. Linear peptide. The linear peptide tasiamide B, produced by the marine cyanobacterium *Symploca* sp., demonstrated high cytotoxicity against both LoVo (IC_{50} = of 3.47 μg/mL) and kB (IC_{50} = 0.48 μg/mL) cancer cells [168]. Since cathepsin D has been shown to be an important target for cancer treatment, tasiamide B derivatives, such as tasiamide B-9, have also shown very potent cathepsin D inhibition in MDA-MB-231 cell line [169].

5.1.1.6. Ketopeptide. Curacin A, a linear compound and a complex hybrid ketopeptide, was identified as the first curacin extracted from the Caribbean cyanobacterium, *L. majuscula* [170,171]. This molecule has

been shown to be the most effective anticancer agent in suppressing A549 cell proliferation, inducing G_2-M cell cycle arrest, and inducing cell apoptosis [172]. Curacin A's mode of action is related to its tubulin-binding potential at the colchicine-binding site, thereby acting as an active competitive antagonist and inhibitor of tubulin polymerization [173]. Due to this activity, it has also shown cytotoxicity against colon, breast, and renal cancer cell lines [171]. The pharmacological effect of curacine A is influenced by several factors, including the presence of high lipophilicity and four double bonds [174].

5.1.1.7. Cyclic depsipeptide

5.1.1.7.1. Apratoxin. Apratoxin isolated from *Symploca* sp. and *Lyngbya* sp. was identified as a valuable natural marine cytotoxic agent, with cancer-fighting ability against different cancer cell lines [175]. More specifically, apratoxin A has anticancer properties by inducing the apoptotic cascade and blocking the cell cycle in the G_1 phase [176]. Its mechanism of action involves blocking the Janus kinase/signal transducer and transcription activator (JAK-STAT) pathway by deregulating the interleukin-6 (IL-6) signal transducer (gp130) and inhibiting the secretory pathway (Fig. 9). This occurs by early blocking co-translational translocation within the secretory process [177]. In addition, apratoxin A, derived from *L. majuscula*, demonstrated significant cytotoxicity against adenocarcinoma cells, exhibiting considerable cytotoxic properties on different human cancer cells, including LoVo cells (IC_{50} = 0.52 nM), kB carcinoma cells (IC_{50} = 0.36 nM), HeLa cells (IC_{50} = 2.2 nM), and U2OS cells (IC_{50} = 50 nM). It affected the secretory pathway of U2OS osteosarcoma cells, leading to G_1 phase arrest in HeLa cervical carcinoma [176]. This compound also induced cell death by specifically inhibiting the translocation pathway of the Sec61 protein [178]. Moreover, apratoxins B and C, from *Lyngbya* sp., showed significant cytotoxicity towards LoVo colon cancer cells (IC_{50} = 10.8 nM) and oral squamous cell carcinoma κB (IC_{50} = 21.3 nM) [179]. Apratoxin D, derived from *Lepista sordida* and *L. majuscula*, also demonstrated considerable cytotoxic effect on the H-460 cell (IC_{50} = 2.6 nM) [178], while apratoxin E, isolated from *L. bouilloni*, exhibited potent antiproliferative potential against epithelial carcinoma HeLa (IC_{50} = 72 nM), osteosarcoma U2OS (IC_{50} = 59 nM), and colon adenocarcinoma HT29 (IC_{50} = 21 nM) [180]. As for Apratoxin F, also from *L. bouilloni*, it demonstrated cytotoxic effect on lung (H-460) (IC_{50} = 2 nM) and colorectal (HCT-116) cell lines (IC_{50} = 36.7 nM). Apratoxin G has also showen cytotoxicity towards the aforementioned tumor cells [181].

5.1.1.7.2. Aurilide. Aurilide extracted from *Dolabella auricularia* induced apoptosis (in vitro) in different human tumor cells, at concentrations ranging from the picomolar spectrum to the nanomolar spectrum. It particularly promoted mitochondria-induced apoptosis by binding to prohibitin-1 and activating optic atrophy-1. Aurilide's mechanism of cytotoxicity is mediated by the apoptosis regulatory protein, PHB1 [182]. Aurilide B and C exhibited cytotoxicity on neuroblastoma and human lung cancer (NCI-H460) cell lines from neuro-2a mice (Aurilide B, NCI-H460: LC_{50} = 0.04 μM; neuro-2a: LC_{50} = 0.01 μM) [33]. Aurilide B exhibited potent cytotoxicity towards human kidney, leukemia and prostate tumor cells from the NCI-60 panel, as well as a panel of 60 human cancer cells obtained from various tissues, with a mean growth inhibition (GI_{50}) value below 10 nM [33].

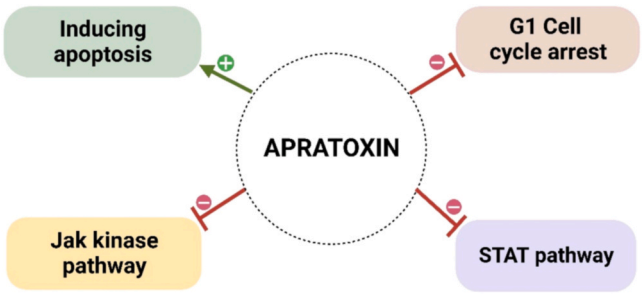

Fig. 9. Anticancer mechanisms of Apratoxin.

5.1.1.7.3. Coibamide A. Coibamide A is derived from *Leptolyngbya* sp. (marine cyanobacterium), which has demonstrated remarkable cytotoxic potential against 60 selective tumor cells, including colon, ovarian, and breast cells. Coibamide A exhibited a potent cytotoxic potential in the MDA-MB-231 tumor cell [45]. This marine bioactive molecule exhibited antiproliferative activity which was linked to G_1 cell cycle arrest. Comparable findings were obtained when coibamide A was administered to glioblastoma cells, including SF-295 and U87-MG. It suppressed the proliferation of human umbilical vein endothelial cell (HUVEC) by inducing morphological changes and downregulating the expression of VEGFR2 [183]. Moreover, coibamide induced cell death by autophagy, independently of the mTOR pathway, in human glioblastoma (U87-MG and SF-295) cells [184]. These data highlight the potential of coibamide A as a promising candidate for the development of therapies specifically targeting cancer cell lines, particularly those implicated in breast, colon, ovary, and glioblastoma.

5.1.1.7.4. Lyngbyabellin. Lyngbyabellin A and B, isolated from *L. majuscula*, exhibit enhanced actin polymerization effect. Lyngbyabellin A showed a mild degree of cytotoxicity towards LoVo human colon cancer (IC_{50} = 0.5 μg/mL) and KB cervical cancer (IC_{50} = 0.03 μg/mL) cell lines [185]. However, Lyngbyabellin B showed stronger cytotoxic effect on these two cells (KB: IC_{50} = 0.10 μg/mL; Lovo: IC_{50} = 0.83 μg/mL). Other members of this family of compounds, namely lyngbyabellin E-I, induced cytotoxic effect on human lung NCI-H460 tumor and mouse neuroblastoma cell lines [186], whereas lyngbyabellin N, derived from *Moorea bouillonii*, showed strong cytotoxicity towards colon tumor HCT116 cell lines (IC_{50} = 40.9 ± 3.3 nM) [187].

5.1.1.7.5. Lagunamide. Lagunamide A, extracted from *L. majuscule* (marine cyanobacterium), presented significant toxicity against various tumor cells, with an IC_{50} range of 1.6–6.4 nM. These lines include P388 murine leukemia, HCT8 human colorectal cancer, A549, SK-OV3, and PC3 cells. Lagunamide A showed anticancer properties on breast tumor MCF7 and HCT8 cell lines, acting through mitochondrial apoptosis [188]. In contrast, lagunamide A and B demonstrated a cytotoxic effect on P388 leukemia cells, with an IC_{50} range of 6.4–20.5 nM [188]. Additionally, lagunamide C, also from *L. majuscule*, has been shown to be extremely cytotoxic towards carcinoma cells (A549, P388, HCT8, SK-OV3, and PC3) [189].

5.1.1.7.6. Cryptophycin. The macrolide depsipeptides cryptophycin 1 and cryptophycin 52 are potent cytotoxic compounds, acting as microtubule inhibitors and having a mechanism of action similar to Vinca alkaloids. Cryptophycin 1, extracted from Nostoc strains, demonstrated an anti-tumor effect against L1210 murine leukemia cells [51]. Its mode of action involves binding to tubulin, thereby altering microtubule assembly [190]. Moreover, it showed increased cytotoxicity towards LoVo and KB cells by promoting apoptosis [191]. Antiproliferative properties were also observed on ovarian carcinoma SKOV3 and breast carcinoma MDA-MB-435 cell lines, leading to G_2/M cell cycle arrest [44]. Additionally, the anticarcinogenic properties of the conjugates iso-DGR-cryptophycin and RGD-cryptophycin were investigated on M21-L and M21 melanoma cells, revealing an anti-tumor effect at different nanomolar concentrations depending on the expression of integrin $\alpha_v\beta_3$ [192].

5.1.1.7.7. Hoiamide. The cyclic depsipeptide hoiamides A and B, obtained from *L. majuscula* and *Phormidium gracile*, exhibited cytotoxicity on numerous tumor cells [193]. Hoiamide A showed moderate levels of cytotoxicity towards human lung adenocarcinoma cells (H460) and mouse neuroblastoma cells (neuro-2a), whereas hoiamide B showed low cytotoxicity towards H460 cells [193]. On the other hand, the cyclic marine depsipeptide homodolastatin 16, extracted from *L. majuscula*, exhibits moderate cytotoxic action on the ME180 cervical cell line and the esophageal cell lines (WHCO6 and WHCO1), with IC_{50} of 8.3, 10.1, and 4.3 μg/mL, respectively [194].

5.1.1.7.8. Largazole. Largazole, a cyclic depsipeptide isolated from

Symploca sp., is a strong class I HDAC inhibitor and is used in the formulation of antitumor drugs. It demonstrated significant efficacy in altering the development of highly transforming invasive MDA-MB-231 cells (IC_{50} = 7.7 nM) [58]. Furthermore, it markedly inhibited the development of neuroblastoma IMR-32 (IC_{50} = 16 nM) and colon HT29 (IC_{50} = 12 nM) cells [58]. Similar pharmacological efficacy was also observed on transformed osteosarcomatous U2OS cells (IC_{50} = 55 nM) [195]. In the HT29 colon cancer cell, largazole induces G_2/M cell cycle arrest [185].

5.1.1.7.9. Majusculamide C. Majusculamide C, a cyclic depsipeptide from *L. majuscula*, has demonstrated strong cytotoxicity on multiple cancer cell lines. It demonstrated potent cytotoxic effect, with IC_{50} values of 0.51 μg/mL for OVCAR-3 (ovarian carcinoma), 0.058 μg/mL for A498 (kidney cancer), 0.0032 μg/mL for NCI- H460 (lung cancer), 0.0013 μg/mL for KM20L2 (colorectal cancer) and 0.013 μg/mL for SF-295 (glioblastoma) [196].

5.1.1.7.10. Obyanamide and palau'amide. Obyanamide, from *L. confervoides*, showed considerable cytotoxic effect on LoVo (IC_{50} = 3.14 μg/mL) and KB (IC_{50} = 0.58 μg/mL) cells [197]. On the other hand, palau'amide a cyclic depsipeptide obtained from *Lyngbya* sp., demonstrated substantial cytotoxic effect towards KB cells (IC_{50} = 13 nM) [198].

5.1.1.7.11. Palmyramide A, and pitipeptolides A and B. Palmyramide A, extracted from *L. majuscula*, showed cytotoxicity on neuro-2a cells (IC_{50} = 17.2 μM). Moreover, it also showed cytotoxic properties against human lung H-460 cell line (IC_{50} = 39.7 μM) [199]. In contrast, pitipeptolides A and B, also cyclic depsipeptides obtained from the same species, revealed cytotoxic potential on colon HT29 cells, with an IC_{50} value of 13 μM for both compounds [200]. Moreover, on LoVo cells, these pitipeptolides (B and A), showed cytotoxicity, with IC_{50} of 1.95 and 2.25 μM, respectively [21].

5.1.1.7.12. Pitiprolamide, tasipeptins A/B and ulongapeptin. Pitiprolamide, tasipeptins (B and A) and ulongapeptin are cyclic depsipeptides extracted respectively from *Symploca* sp., *L. majuscula*, and *Lyngbya* sp. Pitiprolamide revealed its potent anticancer efficacy on colorectal cancer (HCT116) and breast cancer (MCF7) by inducing cytotoxic effect with an IC_{50} value of 33 μM for both cells [201]. As for tasipeptins B and A [202] as well as ulongapeptin [203], they showed marked antiproliferative effects against kB oral epidermoids, increasing cytotoxicity with respective IC_{50} values of 0.83, 0.93, and 0.63 μM.

5.1.1.8. Peptide. Bisebromoamide is a cytotoxic peptide, isolated from *Lyngbya* sp., which demonstrated remarkable anticancer activity on HeLa S3 cells (IC_{50} = 0.04 μg/mL). In addition, this component showed strong inhibition of protein kinases, particularly the phosphorylation of ERKs, in rat kidney epithelial cells (NRKs) by the stimulation of platelet-derived growth factor (PDGF). This specific inhibition was observed after treatment with concentrations ranging from 0.1 to 10 μM of this peptide [204,205].

5.1.1.9. Lipopeptides. Pseudo-dysidenine and dragonamide, two lipopeptides extracted from *L. majuscula*, demonstrated cytotoxicity against A-549, MEL-28, HT-29, and P-388 carcinoma cells with an IC_{50} > 1 μg/mL [206]. In contrast, somocystinamide A, also isolated from the same species, revealed remarkable antiproliferative effects on various cancers. It showed high cytotoxicity against CEM leukemia (IC_{50} = 14 nM), Jurkat (T-cell leukemia, IC_{50} = 3 nM), M21 melanoma (IC_{50} = 1.3 μM), A549 lung carcinoma (IC_{50} = 46 nM), U266 myeloma (IC_{50} = 5.8 μM), and Molt4T leukemia (IC_{50} = 60 nM) cells. Its mechanism of action was related to caspase 8 activation and apoptosis induction [207]. Another lipopeptide called Kalkitoxin, derived from the aforementioned cyanobacterium, also demonstrated anticancer action by reducing the cell survival of HCT116 colon cancer (IC_{50} = 2.7 nM) and T47D breast tumor (IC_{50} = 5.6 nM) cells [208].

5.1.1.10. Other compounds. Grassystatin D and F, two linear depsipeptides, isolated from marine cyanobacteria, strongly inhibited cathepsin D/E proteases with IC_{50} values from 0.1 to 1 μM, specifically targeting TNBC cell migration [209]. Similar results were reported by Catassi [210] using curacin A and dolastatin 10 from *L. majuscula* and *Symploca* sp., respectively, against human A549 lung carcinoma. Furthermore, Simmons et al. [211], evaluated the cytotoxic potential of desmethoxymajusculamide C, from *L. majuscula*, on HCT-116 cell lines using an MTT reduction method. They found that this compound showed selective and potent antitumor effect with an IC_{50} of 20 nM, by modifying the cellular microfilament network.

Symplostatin 1, extracted from *S. hydnoides* cyanobacteria, demonstrated an anticancer effect against breast MDA-MB-435 cell. Its mechanism of action involves induction of apoptosis through micronuclei formation, Bcl-2 phosphorylation, and caspase-3 activation [212].

5.1.2. Antitumor properties of bioactive components from marine microalgae

Various microalgae species contain many bioactive components with promising anti-cancer properties, such as polysaccharides, polyunsaturated aldehydes (PUAs), carotenoids, epimeric carotenoids, fatty alcohol esters, glycolipids, phaeophytins, and stigmasterol (Table 4).

5.1.2.1. Polysaccharide. Polysaccharides derived from microalgae showed successful bio-enhancing activity for a range of industrial applications, although limited investigations were performed on their anticancer potential. The potential activity of these compounds is influenced by their molecular weight and sulfate content, which impacts their effect on cancer cells [214]. Among the most studied microalgal polysaccharides are chrysolaminarin polysaccharide, laminarin, alginic acid and sulfated polysaccharides.

5.1.2.1.1. Chrysolaminarin polysaccharide. Chrysolaminarin polysaccharide is a compound isolated from the diatom *Synedra acus*, belonging to the chrysolaminarin family. A study by Kusaikin et al. [215] evaluated its antitumor effect against colon tumor cells (DLD-1 and HTC-116) using the MTS method. Therefore, promising anticancer activity was recorded, with IC_{50} values of 47.7 μg/mL for DLD-1 and 54.5 μg/mL for HCT-116. Moreover, at concentrations greater than 200 mg/mL, no toxic effects were observed on DLD-1 and HTC-116 cells [215].

5.1.2.1.2. Laminarin. Laminarin, a polysaccharide derived from *Eisenia bicyclis*, brown algae, demonstrated antitumor potency by inhibiting tumor growth and promoting apoptosis. Laminarin also induced sub-G_1 cell cycle arrest in ovarian clear cell carcinoma as well as in papillary adenocarcinoma serous cell lines (OV90), with IC_{50} of 2 mg/mL for theses cells. The underlying mechanism involves blockade of intracellular PI3K/MAPK signaling in ovarian cancer cells, leading to increased cytochrome *c* release, higher DNA fragmentation, and increased expression of apoptosis markers. In addition, laminarin promotes loss of matrix metalloproteinases (MMPs) in carcinoma cells and stimulates autophagy *via* the inactivation of both P62 and ULK1 phosphorylation [216]. In an in vitro experiment, laminarin as well as its sulfated analog demonstrated potentially significant anticancer properties against malignant melanoma SK-MEL-28 as well as mouse epidermal JB6 Cl41 cells. These compounds have shown an ability to suppress migration and proliferation of SK-MEL-28 and JB6 Cl41 cancer cells by down-regulating the ERK1/2 signaling mechanism and inhibiting MMP-2 and MMP-9 proteases [217]. Laminarin also demonstrated cytotoxic effect against many carcinoma cells and suppressed colony formation in colon tumor cells, including DLD 1, HT-29, and HCT-116 [218–220]. In a study by Ji C.F. and Ji Y.B. [221], it was observed that LoVo cell treatment with laminarin for 24 h led to a decrease in pro-caspase-3, − 8, and Bcl-2 expression levels. On the other hand, death receptor 4 (DR4), DR5, tBid, Bid, Bax, TRAIL, and Fas-associated protein with death domain (FADD) were upregulated [221]. The results

Table 4
In vitro investigations and mechanisms of action of extracts and bioactive components extracted from microalgae.

Secondary metabolite (source)	Investigated cell lines	Key results	References
Sulfated polysaccharide			
Fucoidans *(Sargassum horneri, Ecklonia cava, C. costata* and *Fucus vesiculosus*	Human hepatocellular carcinoma cells (Huh7) and HepG2 cells	Huh7: IC_{50} = 2.0 mg/mL; HepG2: IC_{50} = 4.0 mg/mL Inhibited cell proliferation and growth Downregulated chemotaxin CXCL12/ CXCR4 expression	[229]
	Human lung cancer cells (A549)	IC_{50} = 400 μg/mL Suppressed ERK1/2 pathway Inhibited metastatic effect, migration/invasion and PI3K/Akt/mTOR pathway	[228]
	MDA-MB-231 cells	IC_{50} = 820 μg/mL Induced apoptosis Activated caspases and mitochondrial dysfunction Decreased Bcl-2 expression levels	[227]
	SK-MEL-28 and DLD-1 cells	IC_{50} = 100 μg/mL Exhibited anticancer effect	[226]
Polysaccharide			
Chrysolaminarin polysaccharide *(Synedra acus)*	DLD-1 and HTC-116 cell lines	HTC-116: IC_{50} = 54.5 μg/mL DLD-1: IC_{50} = 47.7 μg/mL Inhibited cell proliferation	[214,215]
Carotenoids			
Zeaxanthin (*Isochrysis galbana, Porphyridium cruentum, P. tricornutum, Nannochloropsis gaditana*, and *Tetraselmis suecica*)	HT-29 cells	IC_{50} = 10 μM Induced cytotoxic effect	[234,235]
Siphonaxanthin (*Caulerpa lentillifera, Codium fragile,* and *U. japonica)*	HUVECs	IC_{50} = 2.5 μM Inhibited angiogenic function Suppressed FGF-2, FGFR-1 and EGR-1	[238,239]
	HL-60 cells	IC_{50} = 10 μM Induced apoptosis Enhanced chromatin condensation Decreased Bcl-2 Increased caspase-3 and GADD5α Upregulated DR5	[239]
Fucoxanthin *(Undaria pinnatifida)*	HL-60 cells	IC_{50} = 22.6 μM Inhibited cell proliferation Induced apoptosis Arrested cell cycle at G_0/G_1 phase or G_2/M phase	[60,241]
Neoxanthin (*Tetraselmis suecica)*	A549 and HeLa cell lines	Enhanced cytotoxicity	[246]
Violaxanthin (*Dunaliella tertiolecta)*	MDR1 gene-transfected mouse lymphoma and MCF-7 cells	Inhibited P-glycoprotein (P-gp) and MRP1	[245]
	L1210 human MDR1 gene-transfected mouse lymphoma cells and MDA-MB-231 cells		[244]
	MCF-7 cell line	IC_{50} = 20 and 40 μg/mL Induced apoptosis Increased cytotoxicity	[243]
Glycolipid			
Nigricanosides A and B and methyl esters of nigricanosides A and B (*A. nigricans)*	MCF-7 and HCT-116 cells	Inhibited cell proliferation Exhibited antimitotic activity Increased tubulin polymerization within the cell	[249]
Epimeric carotenoids			
Dinochrome A and B (*Protoperidinium bipes*)	GOTO, osteosarcoma cells (OST), and HeLa cells	GOTO: IC_{50} = 5 μg/mL OST: IC_{50} = 25 μg/mL Inhibited cell proliferation and TPA-stimulated 32 P-incorporation into the phospholipids of HeLa cells	[247]
Fatty alcohol ester			
Nonyl 8-acetoxy-6-methyloctanoate (*P. tricornutum*)	HL-60 and A549 cells Melanoma B16F10 cell line	HL-60: IC_{50} = 65.15 μM A549: IC_{50} = 50 μg/mL B16F10: IC_{50} not specified Promoted apoptosis Arrested cell cycle at the sub-G_1 Phase	[248]
Sterol			
Stigmasterol (*Navicula incerta)*	HepG2 cell line	IC_{50} = 20 μM Increased cytotoxicity Inhibited cell proliferation Induced apoptosis Arrested cell cycle at G_0/G_1 and G_2/M phase Increased caspase-8/− 9 and Bax/p53 Downregulated Bcl-2/XIAP	[6251]
Porphyrin Phaeophytins			
(132-R)-Hydroxyphaeophytin A and B (*C. fasciculatis)* (132-S)-Hydroxyphaeophytin A and B (*C. fasciculatis)* 20-Chlorinated (13^2-*S*)-hydroxyphaeophytin A (*C. fasciculatis)* Porphyrinolactone (*C. fasciculatis*) Anionic polysaccharide	HeLa cell line	IC_{50} = 50 μM Inhibited cell proliferation, NF-κB pathway Inhibited the TNF-α-induced NF-κB translocation	[250]

(*continued on next page*)

Table 4 (*continued*)

Secondary metabolite (source)	Investigated cell lines	Key results	References
Alginic acid (*Sargassum wightii*)	NSCLC-induced angiogenesis	Inhibited cell growth Downregulated VEGF-A/STAT3 expression Activated miR-506 expression	[223]
Xanthophyll carotenoids			
Lutein (*I. galbana*, *Porphyridium cruentum*, *P. tricornutum*, *Tetraselmis suecica*, and *Nannochloropsis gaditana*)	HT-29 cell line	Induced cytotoxicity	[235]
Polysaccharide			
Laminarin (*E. bicyclis*)	Colon cancer cell lines (HT-29, HCT-116, and DLD-1)	IC_{50} = 200 μg/mL Induced cytotoxicity Inhibited colony formation	[218–220]
	Ovarian clear cell carcinoma cells ES2 OV90 cell line	IC_{50} = 2 mg/mL Inhibited cell proliferation and PI3K/MAPK intracellular signaling Induced apoptosis and MMP loss Arrested cell cycle at sub-G_1 Phase	[216]
	Normal mouse epidermal cells JB6 Cl41 SK-MEL-28 cell line	Inhibited cancer proliferation and MMP-2/MMP-9 Downregulated ERK1/2 signaling	[217]
	LoVo cell line	Induced apoptosis Upregulated DR4/DR5/TRAIL/FADD/Bid/tBid/Bax Downregulated pro-caspase-8/pro-caspase-3/Bcl-2	[221]
	HT-29 cell line	IC_{50} = 5 mg/mL Induced apoptosis Arrested cell cycle at sub-G_1 and G_2-M phase Inhibited the heregulin-stimulated phosphorylation of ErbB2 Decreased cellular proliferation	[222]
Polyunsaturated aldehydes (PUAs)			
2-*trans*-4-trans-7-cis-decatrienal 2-*trans*-4-cis-7-cis-decatrienal 2-*trans*-4-*trans*-decadienal	Caco-2 cell line	IC_{50} = 11–17 μg/mL Inhibited cell proliferation Increased cytotoxicity	[232]
2-*trans*-4-*trans*-octadienal (*Skeletonema marinoi*)	A549 cell line	IC_{50} = 5 μM Inhibited cell cycle at either G_1 or S Phase	[231,233]
2-*trans*-4-*trans*-heptadienal (*Skeletonema marinoi*)	Colon COLO 205 A549 cell line	IC_{50} = 10 μM Induced cytotoxicity Inhibited cell cycle at either G_1 or S Phase Upregulated caspase-3/AIFM1	

showed that laminarin suppressed hegulin-stimulated phosphorylation of ErbB2. Cell cycle analysis revealed that laminarin increased sub-G_1 and G_2-M cell proportion. In addition, a reduction in cell proliferation dependent on the activation of suppression on ErbB and the activation of the N-terminal kinase c-Jun was observed [222].

5.1.2.1.3. Alginic acid. Alginic acid is a natural anionic polysaccharide derived from brown seaweed cell walls or seaweed *Sargassum wightii*. This polysaccharide has anti-angiogenic properties, as it suppresses NSCLC-induced angiogenesis by promoting the expression of miR-506. It also decreased VEGF-A expression, an important cytokine involved in the induction of angiogenesis, and decreased the activity of STAT3 [223].

5.1.2.1.4. Sulfated polysaccharide. Sulfated polysaccharide is a major component of *Saccharina japonica* and *Undaria pinnatifida*, two brown algae [224]. It showed anticancer properties by blocking the proliferation of T-47 (breast cancer) and SK-MEL-28 (malignant melanoma) cell lines, while inhibiting colony development [225]. Fucoidans, on the other hand, are sulfated polysaccharides obtained from *Costaria costata*, *Ecklonia cava*, and *Sargassum horneri*. These marine molecules showed promising anticancer effects against DLD-1 and SK-MEL-28 cell lines, with an IC_{50} value of 100 μg/mL for both cell lines [226]. Zhang et al. [227] examined the impact of LMWF on apoptosis of MDA-MB-231 cells. LMWF treatment of MDA-MB-231 cells resulted in caspase activation and mitochondrial dysfunction, particularly dissipation of mitochondrial membrane, release of cytochrome *c*, alteration of Ca^{2+} homeostasis, and inhibition of Bcl-2, Mcl-1, Bcl-xl antiapoptotic protein [227]. Lee et al. [228] demonstrated the antimetastatic action of fucoidan derived from the algae *Fucus vesiculosus* on human lung tumor cells (A549, IC_{50} = 400 μg/mL). Fucoidan also significantly suppressed the PI3K/Akt/mTOR pathway, related to decreased MMP-2 expression levels in A549 cell line. In addition, inhibition of the ERK1/2 pathway has been found to contribute to this antimetastatic action [227]. In evaluating the effects of fucoidan on chemokine ligand 12 (CXCL12)/chemokine receptor 4 (CXCR4) expression and its anticancer potential on hepatoma Huh7 cells, Nagamine T. et al. revealed that this sulfated polysaccharide dose-dependently inhibited the growth of HepG2 (IC_{50} = 4.0 mg/mL) and Huh7 (IC_{50} = 2.0 mg/mL) cells [229]. Furthermore, fucoidan extracted from the microalgae *U. pinnatifid* induced apoptosis in A549 cells by reducing the expression of Bcl-2, procaspase-3, and PARP cleavage, while activating the pro-apoptotic protein Bax [230].

5.1.2.2. Polyunsaturated aldehydes (PUAs). Miralto et al. [231] revealed that PUAs (2-trans-4-trans-decadienal, 2-trans-4-trans-7-cis-decatrienal, and 2-trans-4-cis-7-cis-decatrienal) isolated from diatoms *Skeletonema costatum*, *Thalassiosira rotula*, *Pseudo-nitzschia delicatissima*, and *Phaeocystis pouchetii* exhibited high cytotoxic activity and potent antiproliferative effect on colon cancer in Caco-2 cell line [231,232].

Sansone et al. [233] studied the impact of three other PUAs, namely 2-trans-4-trans-decadienal, 2-trans-4-trans-octadienal, and 2-trans-4--trans heptadienal, extracted from the marine diatom *S. marinoi*, on A549 and COLO 205 cells. Among these compounds, 2-trans-4-trans-heptadienal and 2-trans-4-trans-octadienal exhibited potent cytotoxicity against lung (IC_{50} = 5 μM) and colon (IC_{50} = 10 μM) cancer cells [233]. In addition, these compounds promoted apoptosis, as evidenced by the condensation of chromatin, lack of membrane stability, and nuclear fragmentation. In all cancer cells, they also induced G1/S cell cycle arrest and were related with up-regulation of apoptosis-inducing factor 1 (AIFM1) and caspase-3 [233].

5.1.2.3. Carotenoids

5.1.2.3.1. Zeaxanthin and lutein. Zeaxanthin (carotenoid) is found in a variety of microalgae including *Nannochloropsis gaditana*, *I. galbana*, *P. cruentum*, *T. suecica*, and *P. tricornutum* [234]. Zeaxanthin showed cytotoxic effect on HT-29 cell line (IC_{50} = 10 μM), while it did not show

significant cytotoxicity on colon epithelial (CCD 841 CoTr) cell line [235]. Similarly, lutein, another carotenoid, also showed anticancer activity [235,236]. These findings suggest that zeaxanthin and lutein may have potential application in the field of cancer control.

5.1.2.3.2. Siphonoxanthin. Siphonoxanthin extracted from *Umbraulva japonica*, *Codium fragile* and *Caulerpa lentillifera* (all are green algae). Siphonoxanthin has been shown to have antitumor potential against the human leukemia HL-60 cell line (IC_{50} = 10 μM) by inducing apoptosis, accompanied by intrinsic chromatin condensation, decreased Bcl-2 expression, and elevated caspase-3 activation [237]. Furthermore, the expression levels of DR5 and GADD5α were significantly increased [237]. Siphonoxanthin has also demonstrated antiangiogenic activity using HUVECs and rat aortic rings [238]. It diminished the mRNA expression levels of fibroblast growth factor receptor (FGFR-1), fibroblast growth factor 2 (FGF-2), and early growth response 1 (EGR-1) [237,239].

5.1.2.3.3. Fucoxanthin. Fucoxanthin, a major brown algal carotenoid belonging to the xanthophyll pigment family, is present in marine microalgae and macroalgae [240]. Research by Hosokawa et al. [241] proved that fucoxanthin from *U. pinnatifida* exhibited a potent anti-proliferative activity on HL-60 cell line by inducing apoptosis [241]. Fucoxanthin has been widely studied for its anti-cancer potential, and various investigations have revealed that it inhibits tumor cell proliferation by apoptosis and blocking the cell cycle in G_2/M or G_0/G_1 phase *via* different molecular pathways. This cytotoxic action involves interference with the proteins; NF-κB, MAPK, Bcl-2, GADD45, caspase-3, −8, and-9. The expression levels of these proteins were significantly affected by fucoxanthin [60]. Among the various carotenoids studied, fucoxanthin was particularly investigated as a potential candidate for anti-carcinogenic applications and has demonstrated substantial anticancer properties [60,242].

5.1.2.3.4. Violaxanthin. Violaxanthin, the main active metabolite contained in the dichloromethane extract of the green alga *D. tertiolecta*, was studied by Pasquet et al. [243] for its anticancer potential on four distinct cancer cells, namely MDA-MB-231, MCF-7, LNCaP, and A549. Their findings revealed that violaxanthin induced early cell death, characterized by biochemical and morphological alterations, in the MCF-7 cell line, without affecting DNA fragmentation. Additionally, this compound showed multidrug resistance (MDR) reversal properties by blocking both MRP1 and P-gp in L1210 cells (mouse lymphoma cells) and MDA-MB-2 cells [244]. Similar results were obtained when violaxanthin reversed MDR in MCF-7 cells and MDR1 (gene-transfected mouse lymphoma) [245]. These observations demonstrate the potential of violaxanthin as a promising anticancer agent and its capacity to counter drug resistance in certain cancer cell lines.

5.1.2.3.5. Neoxanthin. Neoxanthin, a xanthophyll carotenoid isolated from *T. suecica*, demonstrated remarkable cytotoxicity towards tumor cells. Of the four xanthophylls tested, 9-Z-neoxanthin showed the highest efficacy in reducing the viability of cervical HeLa (IC_{50} = 3.8 μM) and lung A549 (IC_{50} = 7.5 μM) cancer cells [246].

5.1.2.4. Epimeric carotenoids. Dinochromes B and A are carotenoid epimers derived from the marine red-tide *Peridinium bipes*. These compounds demonstrated significant anti-cancer properties by suppressing the proliferation of neuroblastoma (GOTO, IC_{50} = 5 μg/mL), osteosarcoma (OST, IC_{50} = 25 μg/mL) cell lines [247].

5.1.2.5. Fatty alcohol ester. Nonyl 8-acetoxy-6-methyloctanoate is an ester obtained from *P. tricornutum*. This molecule showed inhibitory activity on A549 cell growth (IC_{50} = 50 μg/mL) as well as on human promyelocytic leukemia cell (HL-60, IC_{50} = 65.15 μM). Its anticancer effects have been associated with increased apoptosis, sub-G_1 cell cycle arrest, and DNA damage. Furthermore, this molecule upregulated the expression of Bax, a pro-apoptotic protein, and the caspase-3 and p53 proteins, while suppressing Bcl-xL, an anti-apoptotic protein [248].

5.1.2.6. Glycolipid. Nigricanosides B and A, as well as the corresponding methyl esters, are glycolipids extracted from *Avrainvillea nigricans*. These molecules have been the subject of much research because of their anti-cancer properties. Indeed, investigations showed that these glycolipids inhibit the proliferation of HCT-116 cells as well as human breast cancer cells (MCF-7). In addition, they have shown antimitotic action by inducing tubulin polymerization in cells [249].

5.1.2.7. Pheophytins. Pheophytins are porphyrin-containing heterocyclic organic compounds. Different pheophytins, such as (132-S)-hydroxyphaeophytin A, (132-R)-hydroxyphaeophytin A and B, porphyrinolactone, as well as (132-S)-hydroxyphaeophytin A and B, were obtained from *Cladophora fascicularis* (marine green alga). These pheophytins demonstrated anticancer activity by suppressing NF-κB activation in the HeLa cell by blocking TNF-α-induced NF-κB translocation from the cytoplasm to the nucleus [250].

5.1.2.8. Stigmasterol. Kim et al. extracted stigmasterol from a benthic microalga, *Navicula incerta*. This compound has demonstrated anticancer properties against the human liver carcinoma ($HepG_2$) cell by inducing apoptosis through several mechanisms. Stigmasterol disrupted mitochondrial membrane potential, causing DNA damage and morphological changes. In addition, it reduced anti-apoptotic proteins, including Bcl-2 and XIAP (X-linked inhibitor of apoptosis protein) (Fig. 10), while caspase-8, −9, p53, and Bax expressions were upregulated. Accordingly, stigmasterol induced G_2/M and G_0/G_1 cell cycle arrest by disrupting essential cellular constituents [6,251].

5.1.2.9. Other compounds. Desai et al. [252] demonstrated the anticancer activity of cytarabine, a nucleoside isolated from *Cryptotheca crypta* microalgae. Cytarabine showed promising cytotoxicity on acute myeloid leukemia (AML) cells (IC_{50} = 272 ng/mL).

Using the same cancer cell, Stengel et al. [253] showed the properties of phycoerythrin isolated from *Lyngbya* sp., a microalgae. This phycoerythrin reduced cell viability in a concentration-dependent way, as well as an alteration of the potential of the mitochondrial membrane, thus contributing to induce G_0/G_1 cell cycle arrest.

5.2. *In vivo investigations and mechanisms of action*

Previous investigations demonstrated the promising activity of zeaxanthin in inhibiting tumor development in animal models. In a study by Nishino et al. [254], it was found that zeaxanthin could prevent spontaneous liver cancer in male mice. Additionally, in mouse lymphoma cancer, zeaxanthin has been shown to reverse multidrug resistance [244]. In another study by Xu et al. (2015) [255], intraocular administration of zeaxanthin to mice has been shown to effectively inhibit tumor growth, invasion and proliferation of uveal melanoma cells in a mouse model. In contrast, another xanthophyll, lutein, also showed significant effects on 4T1 murine mammary carcinoma growth in mice when received a dose of 50 mg/kg/day [256]. Furthermore, a low-dose diet of 0.002 % lutein was associated with decreased tumor incidence, growth, and development in BALB/c mice [257].

Stigmasterol, a bioactive compound in microalgae, showed promising antitumor effects in a study using mice with Ehrlich's ascites carcinoma (EAC). In this xenograft model of human CCA cell lines, this phytosterol significantly inhibited angiogenesis, tumor development, and macrophage recruitment. These effects were obtained through a modulation of the production of pro-inflammatory mediators, suggesting its pivotal function in the suppression of malignant tumors and the regulation of endothelial morphogenesis *via* the TNF-α-VEGFR-2 pathway [258]. Moreover, in a study by Ghosh et al. (2011) [259], stigmasterol was shown to have chemopreventive properties in mice with EAC tumors. This intervention significantly reduced tumor size as well as viable cell number. Moreover, stigmasterol treatment

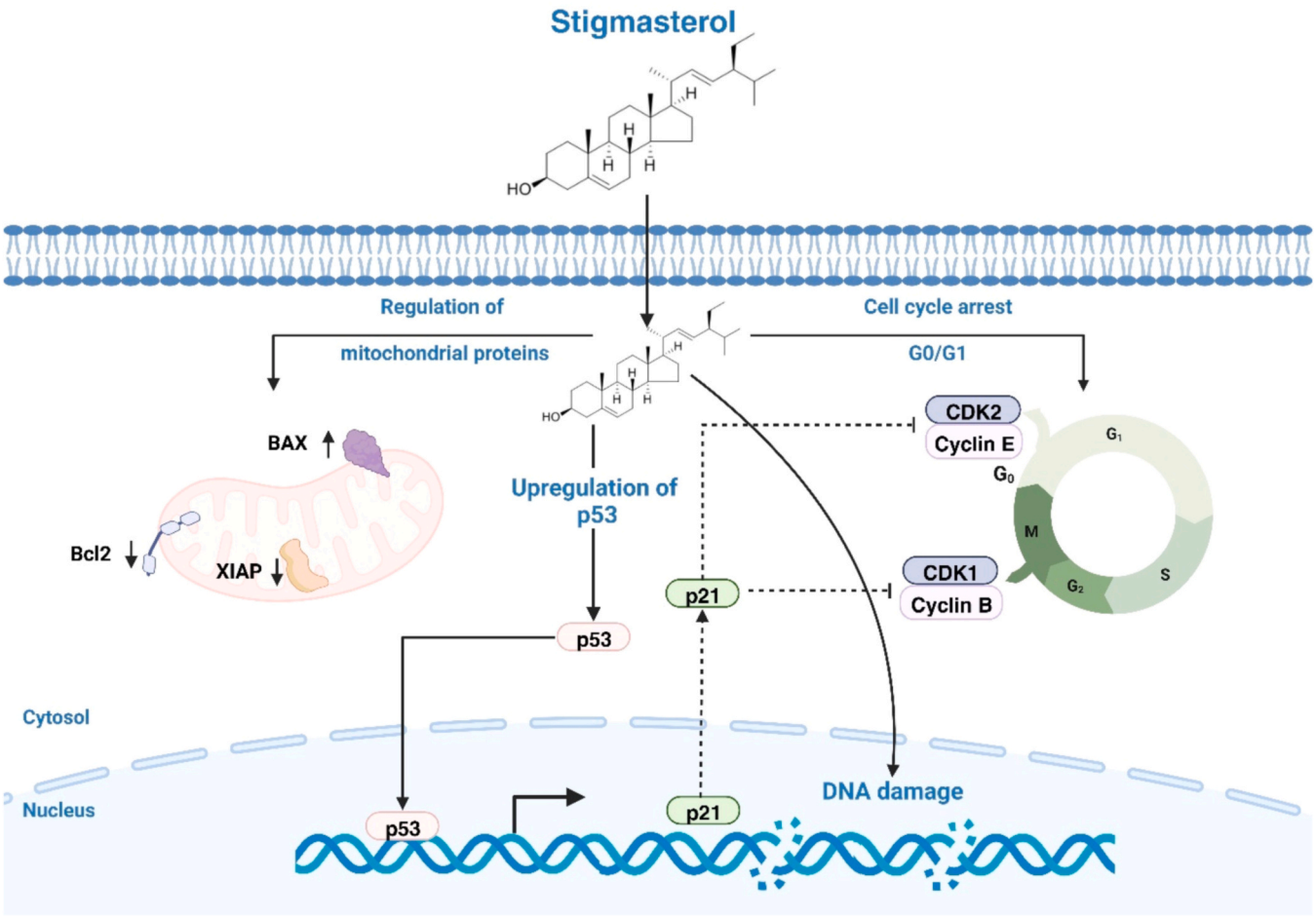

Fig. 10. Anticancer mechanisms of stigmasterol.

(10 mg/kg) decreased lipid peroxidation levels by 56.1 %, compared with the untreated group. Stigmasterol also improved enzymatic antioxidant defenses by upregulating levels of antioxidant enzymes, namely catalase (CAT), glutathione (GSH), and superoxide dismutase (SOD), suggesting its role in preventing carcinoma-induced oxidative stress in mice. As evidenced by hematological investigations, this compound displays a protective role in the hematopoietic system; it augmented hemoglobin (Hgb) levels, platelets, and erythrocyte count, while a significant decrease was noted in blood cell count with a particular enhancement in lymphocytes and monocytes in animals [259]. This effect was dose-dependent compared to untreated mice. Stigmasterol also significantly enhanced LDH activity in ascetic fluid and decreased membrane microviscosity [259]. Taken together, these findings provided a solid foundation for stigmasterol development as an anticancer drug.

Largazole, isolated from cyanobacteria of the genus *Symploca*, demonstrated effective anticancer effect in murine xenograft models of colon cancer HCT116 [58]. It reduced tumor growth by inducing cell apoptosis and causing histone hyperacetylation. Salvador et al. [260] recorded that oral administration of largazole and certain analogues in murine xenograft models (A549 and HCT116 cells) significantly suppressed tumor growth and proliferation.

In contrast, Nishino et al. [261] demonstrated that fucoxanthin exhibits inhibitory properties of spontaneous hepatic tumorigenesis in male C3H/He mice, as well as an antitumor effect in a two-stage carcinogenesis experiment involving ICR mouse skin induced by mezerein and 12-O-teradecanoylphorbol-13-acetate. In this respect, research by Kim et al. [262] demonstrated that fucoxanthin suppresses colonic carcinogenesis in mice induced by 7,12-dimethylbenz[*a*]anthracene. Moreover, this marine carotenoid significantly inhibited, in mice, duodenal carcinogenesis caused by N-ethyl-N′-nitro-N-nitrosoguanidine [263]. Kim et al. [264], the antitumor potential of fucoxanthin on melanoma growth in mice was investigated. Consequently, intraperitoneal administration of this compound resulted in a significant (5-fold) reduction in the volume of B16F10 melanoma tumor implanted in mice, compared to the untreated group. To shed light on the mechanisms underlying the antitumor activities of fucoxanthin, Mei et al. [265] investigated its effect on apoptosis of A549 cells in nude mice. Fucoxanthin caused significant tumor cell apoptosis as evidenced by TUNEL staining analysis. This effect was associated with decreased Bcl-2 expression level and upregulation of caspase-3 [265].

The NF-κB pathway plays an essential role in regulating various key factors involved in tumor initiation, proliferation, and metastasis, including MMPs, iNOS, TNFα, cyclooxygenase-2 (COX-2), IL-8, and other proteins. Dietary astaxanthin, at a concentration of 200 ppm, has been shown to inhibit colitis-related colon carcinogenesis in mice by targeting the NF-κB signaling axis. This carotenoid downregulated mRNA expression levels of IL-1β, COX-2, and IL-6 [266]. In addition, apratoxin reduced the expression level of VEGF-A as well as receptor tyrosine kinases in a colorectal tumor xenograft model [267].

Several in vivo investigations have been performed to assess the efficacy of fucoidan in the treatment of cancer. Zhu et al. (2013) [268] reported the intraperitoneal administration of fucoidan (200 mg/kg) suppressed hepatocellular carcinoma growth and development in a mouse xenograft model. Likewise, in a lung adenocarcinoma model established by inoculating C57BL cells into nude mice, treatment with fucoidan (25 mg/kg) reduced tumor growth rate, proliferation, and metastasis [269]. Moreover, fucoidan demonstrated strong inhibition of

4T1 tumor cells and significantly reduced metastatic tumor nodules in a mouse xenograft model of 4T1 lungs [270]. To identify the possible mechanisms by which fucoidan exerts its antitumor properties, Takeda et al. (2012) [271] elucidated the potential of this molecule on tumor growth, proliferation, and apoptosis. They revealed that fucoidan suppressed the growth of sarcoma 180 cells implanted in mice by stimulating the release of nitric oxide (NO) from activated macrophages, leading to the induction of apoptosis [271]. Collectively, these findings provided important insight into the beneficial health effect of fucoidan in the management of tumorigenesis and metastasis, suggesting its further application as an anticancer agent.

6. Conclusion and perspectives

In this review, our focus has been on exploring bioactive molecules from cyanobacteria and microalgae as anticancer agents. These microorganisms are full of various secondary metabolites, namely flavonoids, terpenoids, and phenolic acids. Pharmacological investigations have demonstrated interesting effects both in vivo and in vitro of these microalgae and cyanobacteria. However, anticancer tests remain mainly limited to in vitro approaches and a few in vivo tests, while clinical trials are still rare and little explored. Any research project aiming to explore the anticancer potential of these bioactive molecules should imperatively study their clinical aspect and evaluate their toxicity in order to validate their clinical efficacy and confirm their harmlessness. Extensive clinical studies are needed to allow a better understanding of their therapeutic potential and pave the way for new cancer treatment strategies.

The phytochemical study of microalgae and cyanobacteria should be extensive, also emphasizing the characterization of other compounds such as minerals and other nutrients. This will suggest their use for nutritional purposes as preventive approaches against cancer risk factors, as well as for therapeutic purposes in patients with certain types of cancer. Nutritherapy is emerging as a new approach, aiming to develop molecules that are both nutritious and therapeutic. By incorporating supplements based on microalgae and cyanobacteria, we could develop functional products aimed specifically at fighting human cancers. Such an approach could open new perspectives in the field of cancer prevention and treatment by exploiting the potential of marine microorganisms and their beneficial compounds. Further research is needed to better understand the mechanisms of action of these molecules and their impact on human health, in order to develop effective and safe interventions to fight cancer.

The richness of microorganisms in bioactive molecules varies from one strain to another and depends on the environmental conditions in which these species thrive. Consequently, the qualitative and quantitative improvement of these secondary metabolites, as well as other mineral and nutritional compounds, will play an essential role in fully valuing these microorganisms. Studies to optimize the production of these beneficial compounds are needed to fully exploit their potential as sources of promising therapeutic and nutritional molecules. These advances will help develop more effective and safe functional products that can be used in the treatment and prevention of various diseases, including cancer. By investing in research and expanding our knowledge of these microalgae and cyanobacteria, we can pave the way for new opportunities in medicine and nutrition to improve the health and well-being of humanity.

CRediT authorship contribution statement

Abdalla Ashraf N: Software, Supervision, Writing – original draft. **Goh Khang Wen:** Project administration, Resources, Software, Visualization, Writing – original draft. **Ming Long Chiau:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. **Bouyahya Abdelhakim:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft. **Goh Bey Hing:** Resources, Writing – review & editing. **Bakrim Saad:** Project administration, Resources, Software, Writing – original draft. **Aanniz Tarik:** Investigation, Visualization, Writing – review & editing. **Chamkhi Imane:** Methodology, Validation, Writing – review & editing. **Taha Douae:** Investigation, Methodology, Writing – original draft. **El Omari Nasreddine:** Project administration, Validation, Writing – review & editing. **El Mneyiy Naoual:** Methodology, Project administration, Visualization, Writing – review & editing. **El Khachlafi Naoufal:** Formal analysis, Visualization, Writing – original draft. **El-Shazly Mohamed:** Investigation, Validation, Writing – original draft. **Khalid Asaad:** Investigation, Methodology, Writing – original draft.

Declaration of Competing Interest

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.

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors extend their appreciation to the Deputyship for Research and innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number (ISP23-81).

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