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REVIEW

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Anticancer potential of algae-derived metabolites: recent updates and breakthroughs

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Abstract

Background Cancer is an increasing medical condition that poses a threat to worldwide populations, despite improvements in scientific research. For normal cancer treatment, a variety of chemotherapeutics, radiation, and medications are available; however, recurrent side effects and multi-drug resistance have limited treatment options and harmed our immune system. Marine algae are a promising source of novel components for the development of new complementary and alternative medications with anti-carcinogenic properties.

Results In this review, we discussed several breakthrough studies on the anti-carcinogenic effects of several macro- and micro-algal components, demonstrating the inhibition of cancer cell development via multiple mechanisms. These components, often referred to as algal biopolymers, have been demonstrated to exhibit a wide range of chemical compositions and physical properties; as a result, they are used in pharmacological, pharmaceutical, nutraceutical, and microbiological applications in different sectors. Moreover, treatment of antimicrobial-resistant *Helicobacter pylori* infection-derived gastric cancer prevention may benefit from the use of algae in addition to standard antibiotics. Additionally, in recent years, it has been shown that algae have incredibly promising low-cost biomedical potentials as therapeutic applications for the treatment of cancer.

Conclusion In recent years, several preclinical studies with the algal bioactive components in the field of novel drug discovery substituting synthetic drugs have been conducted. To demonstrate their potential anticancer actions on various cancerous signaling pathways and consequently reduce cancer, the enormous plasticity of these algae biopolymers has been intensively explored.

Keywords Cancer, Macroalgae, Microalgae, *Helicobacter pylori*, Marine biotechnology, Biomedical approaches, Cancer therapy

Background

Cancer is the world's second most prevalent debilitating disease, accounting for a significant share of all deaths. The multifactorial etiology of cancer encompasses a wide range of illnesses connected to the body's uncontrolled cell development [1]. The three cancer kinds that account for the bulk of instances worldwide are breast, lung, and colorectal cancers [2]. According to the International Agency for Cancer Research, 19.3 million cases of cancer were reported in 2020, and by 2040, that figure is expected to rise by 47% to 28.4 million cases [3]. Furthermore, facilitating replicative immortality, boosting angiogenesis, evading growth promoters, prolonging proliferative signals, resisting cell death, and initiating metastasis and invasion are all trademarks of cancer malignancy [4]. Although the development of new chemotherapeutic drugs for cancer treatment is crucial for halting the disease's progression, improving cancer therapies remains a challenging undertaking [5]. Chemotherapeutic resistance is a key barrier in the treatment of

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various cancers, as a large proportion of tumors relapse and develop resistance, inevitably leading to multi-drug resistance following exposure to multiple anticancer medications with similar structures and modes of action [6]. Over 195,000 plant-derived bioactive components have been identified as preventing cancer growth, either directly or indirectly through immune system activation [7]. The taxonomically diverse marine flora (microalgae, macroalgae, cyanobacteria, bacteria, actinobacteria, fungi, and other halophytes) constitute over 90% of the oceanic biomass offering a great scope of novel anticancer drugs [8]. Similarly, bioactive components found in algae have recently been identified as having anticancer properties by inducing apoptosis and suppressing cell divisions through interfering with signaling pathways [9]. Although, due to a lack of ethnomedical history, the creation of novel components from marine flora is still in its initial phases, leaving them under-represented in today's pharmacopeia [8]. Algal metabolites, also known as algal biopolymers, have been demonstrated to contain a diverse spectrum of chemical compositions and physical properties, and are thus used in pharmacological, pharmaceutical, nutraceutical, and microbiological applications in different sectors [10]. Later bioactive components found in algal metabolites (polysaccharides, proteins, polyunsaturated fatty acids (PUFAs), phycocolloids, vitamins, soluble dietary fibers, phycobilins, carotenoids, phycocyanins, minerals, tocopherols, and terpenes) have been shown to have biological therapeutic potential [11]. Further, the algae-derived bioactive components were later identified to antagonize cancer malignancy hallmarks [12]. Microalgae and macroalgae are the two types of algae that live in the sea. Microalgae are photosynthetic autotrophic microorganisms that contribute significantly to the marine food chain [13]. Of the top 10 producers, China leads with 54,850 tonnes, followed by Chile, Greece, Tunisia, Burkina Faso, Central African Republic, Chad, Bulgaria, and Spain. The total output of microalgae is expected to reach 56,456 tonnes globally [14]. They have been demonstrated to have substantial nutraceutical and therapeutic potential due to their high bioactive metabolite content [13]. Along with, cyanobacteria (blue-green algae), *Spirulina* sp., and *Nostoc* sp. bioactive components have medicinal values [15]. Furthermore, around 5000 years ago, Chinese physicians began using seaweeds, which are macroalgae that predominate the marine flora [13, 16]. The abundance/production of macroalgae worldwide is estimated at 35,762,504 tonnes (wet weight), with Asia contributing the majority of that amount (97.38%), followed by the Americas, Europe, Africa, and Oceania at estimated 1.36%, 0.80%, 0.41%, and 0.05%, respectively [14]. The potential for seaweeds to be used as several therapeutics has piqued the interest of scientists over thirty years. Additionally, seaweeds' medicinal and nutraceutical properties have been applied to the treatment of a number of diseases (stomach ailments, renal disorders, cancer, psoriasis, arteriosclerosis, lung diseases, cancer, gall stones, ulcers, heart disease, and scabies) [13, 17]. Overall algae are known to exhibit anti-tumor, anti-viral, antimicrobial, immune-boosting, and anti-inflammatory activity [15]. Although various research literature works have looked at the potency of anticancer substances, in this article we have focused on the comprehensive anticancer effectiveness of bioactive components derived from algae against a variety of cancer signaling pathways, including gastric cancer caused by the *Helicobacter pylori* bacteria, as well as various cutting-edge techniques in biomedical applications. Alongside, in this review, many other neoplastic indicators are highlighted in silico, in vivo, and in vitro for the identification of novel pharmaceuticals and biomedical treatments to be used in algae-derived cancer therapy in the near future (Figs. 1, 2).

Main text

Cancer biology: a molecular immunopathology

Cancer in humans has been prevalent for a long time, even before the advent of innovation and the use of synthetic substances. Percivall Pott discovered the first evidence of cancer in 1775 when he associated scrotal cancer and chimney soot. However, with the creation of improved scientific investigations, the mechanism of carcinogenesis has been widely studied. In 1971, a war on cancer was declared with the goal of generating new treatments [28, 29]. Cell division is the key phenomenon in the development of a living organism. Approximately 10^{15} cells are present in an adult human which exhibits cell turnover and regeneration due to the presence of stem cells having compartments with approximately 10^{12} divisions/day. Throughout an individual's life, several overlapping biological pathways regulate cell differentiation, balancing the ratio of cell proliferation and apoptosis. Any disruption in homeostasis causes neoplasia or uncontrolled cell proliferation [30]. Cancer has traditionally been studied through the lens of Darwin's three fundamental contextual evolutionary principles (variation, heredity, and selection), which Peter Nowell postulated to be an evolutionary process after analyzing carcinogenesis in advanced malignancies [31]. Furthermore, the mathematical idea of Darwinian evolution has been widely employed to comprehend somatic selection, diversity, and extinction [28]. A succession of gene mutations disturbs cellular function and creates gene dysfunction, resulting in cancer [18].

The intrinsic and non-intrinsic factors that link them to deoxyribonucleic acid (DNA) damage impacting

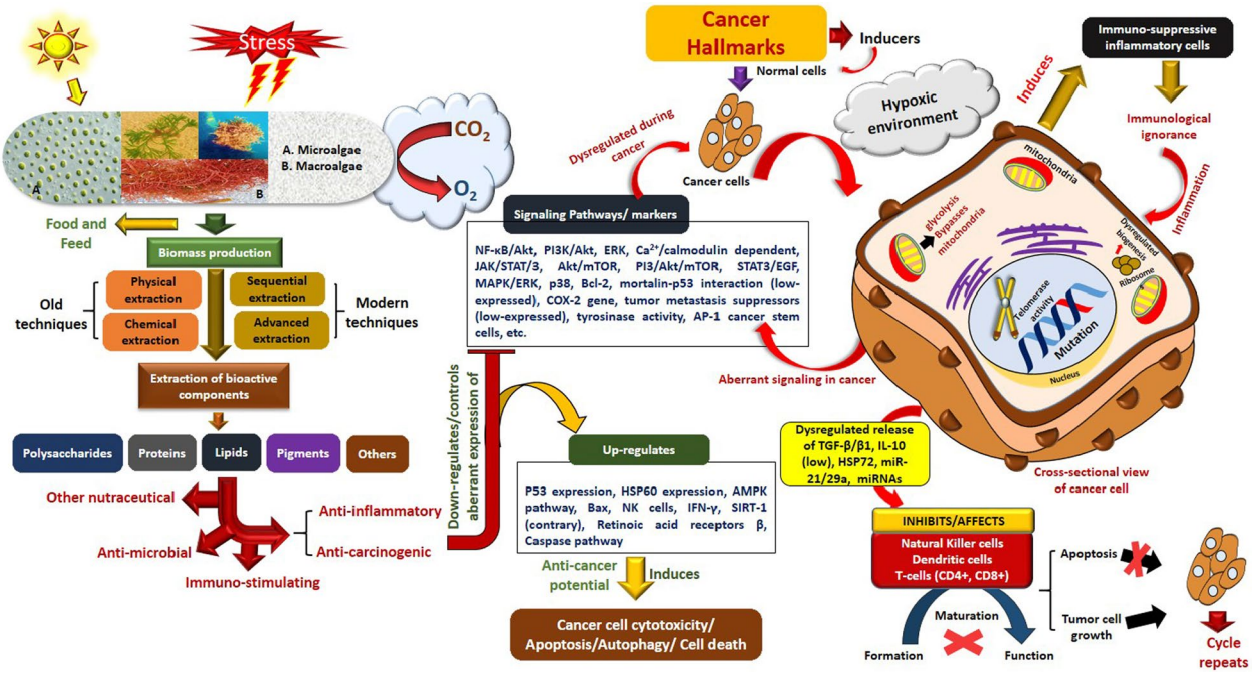

Fig. 1 Mechanism of action of algal bioactive components with anticancer potential via regulating the aberrant expression of cancer signaling pathways. Following a thorough analysis of the literature from articles, the figure is illustrated schematically [18–21]

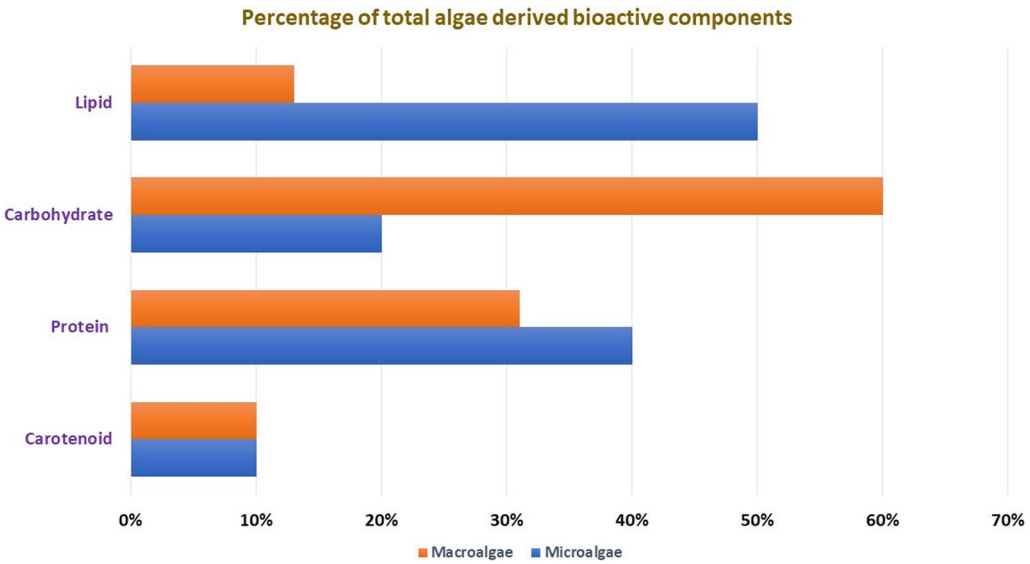

Fig. 2 Percentage of total algae-derived bioactive components [22–27]

cellular homeostasis due to discordant signaling pathways substantially influence the underlying etiology of carcinogenesis [32]. Random replication mistakes owing to spontaneous mutation are intrinsic factors, whereas proto-oncogene mutations are non-intrinsic factors. Radiation, chemical carcinogens, xenobiotics, a terrible routine, viruses, and other external and endogenous causes (hormone levels, abnormal immune system, biological metabolism, repair machinery, etc.) [32, 33]. Chemical carcinogens or xenobiotic components directly or indirectly affect the cellular cytoplasm and/or nucleus which induces proto-oncogenes leading to genetic disorders and mutations [18]. Apart from these carcinogenic factors, infectious oncogenic pathogens contribute 15%

of global malignant tumor heterogeneity responsible for thousands of neoplasias [34]. Bacteria, helminths, and fungi cause inflammation and disease-mediated cancer, whereas oncoviruses cause carcinogenesis by oncogene integration with the host genome [35]. The oncopathogens in humans mostly cause organ-specific or site-specific carcinoma. Therefore, the virus-induced cancers include Human papillomavirus (HPV) which causes oropharyngeal, cervical, anal, and penile cancer; Human T-cell leukemia virus (HTLV)-1 which causes adult T-cell leukemia-lymphoma; Hepatitis B virus (HBV) which causes non-Hodgkin lymphoma, breast, hepatocellular, and pancreatic cancer; Hepatitis C virus (HCV) which causes non-Hodgkin lymphoma, thyroid, and liver cancer; Human immunodeficiency virus (HIV) which causes Kaposi sarcoma, non-Hodgkin lymphoma, lung, liver, anal, and oropharyngeal cancer; Epstein–Barr virus (EBV) which causes Burkitt's lymphoma, gastric, smooth muscle, and nasopharyngeal cancer. *Helicobacter pylori* confer bacterial-induced carcinoma that causes gastric and pancreatic cancer. Among fungi, *Aspergillus* sp. causes liver cancer, and *Candida* sp. causes oral and lung cancer. Various helminths such as *Schistosoma haematobium*, *Schistosoma japonica*, *Schistosoma mansoni*, *Plasmodium falciparum*, *Clonorchis sinensis*, and *Opisthorchis viverrini* are also known to cause cancer [34, 35].

Overall oncogene activation is caused by mutations arising due to erroneous genetic alterations such as point mutations (*G12V Ras* gene), insertional inactivation (*C-myc* gene), deletion (*Erb-B* gene), amplification (*N-myc*), hypomethylation, hypermethylation, deacetylation, and chromosomal translocation (*Abl* and *Bcr* gene) [18, 36]. Furthermore, epigenetic silencing, promoter methylation, and the production of oncometabolite all play a part in oncogenesis [36]. In addition, under normal conditions, including the p21 gene, the p53 gene on human chromosome 17 favorably regulates DNA metabolism, cell differentiation, and cell death. When the p53 gene is altered, cancer cells in the G1 and G2 phases of the cell cycle are generated, followed by a relationship between cyclin-dependent kinase (CDK)1-P2 and cell division cycle (CDC)2. The p53 protein binds to DNA after other genes have produced DNA damage, causing the WAF1 gene to be stimulated. This action causes p53 to bind to CDK2, which then blocks the effect of p21 for the following juncture of the cell cycle. Furthermore, the anticancer effect of p53 causes apoptosis in addition to stopping the cell cycle throughout the G1/S phase [18]. The dysregulation, progression, and dissemination of cancer cells are fueled by several signaling pathways such as receptor-tyrosine kinase mitogen-activated protein /rat sarcoma virus /receptor tyrosine kinase (MAP/RAS/RTK)-kinase signaling, Hippo signaling, Notch signaling, Phosphoinositide 3-kinase (PI3K) signaling, oxidative stress response/Nrf, transforming growth factor-beta (TGFβ) signaling, PI3K-Akt signaling, nuclear factor-kappa B (NF-κB) signaling, β-catenin/wnt signaling, Jun N-terminal kinases (JNK)/p38 signaling, and Ras-extracellular signal-regulated kinase (Ras-ERK) signaling [36–38]. Carcinomatous signaling pathways were activated by these alterations, causing cancer cells to stop dying and proliferate by supplying them with extra metabolites [39]. These cancer cells spread and migrate by accessing the extracellular matrix (ECM), which leads to circulation by alternate migration such as collective cell, mesenchymal, and amoeboid cell migration, despite the fact that they are rarely investigated [40].

Cancer development eludes immune monitoring due to immune checkpoint dysregulation caused by malignancies. Furthermore, immune factor activity is suppressed by hyperactivation of signal transducer and activator of transcription (STAT)-3, a signal transducer and activator of transcription [41]. Both STAT-3 and NF-κB activate anti-apoptotic proteins (B-cell lymphoma (Bcl-2 and Bcl-XL)) that enhance tumor growth by interfering with p53 [42]. Neutrophils are a controversial topic due to their dual function, i.e., tumor-promoting and attacking plasticity. Angiogenesis, metastasis, and immunosuppression are all facilitated by tumor-associated neutrophils (TAN) [43]. Simultaneously, tumor-associated macrophages (TAM) inhibit T-cell and natural killer (NK) cell proliferation by releasing cytokines and immune-suppressive factors thereby stimulating tumor progression [44]. Cancer initiation, progression, and metastasis are all influenced by inflammation. Several mediator molecules, including tumor necrosis factor (TNF-α), NF-κB, and signaling pathways, link inflammation and cancer [45]. Inflammation promotes cancer cell proliferation by raising mutation rates, which are mostly caused by chemical carcinogens and pathogenic microorganisms [42]. Tumor cells boost neutrophil production by secreting growth factors (interleukins (IL)-3, granulocyte–macrophage colony-stimulating factor (GMCSF), and granulocyte colony-stimulating factor (GCSF) or inflammatory cytokines (IL-1/6/17 and TNF-α), which promote tumor progression by inducing cancer-related inflammation. Anti-tumor responses are mediated by TANs, which destroy tumor cells [43, 46]. Alongside, macrophages, dendritic cells, B cells, and T cells also exhibit dual functions as neutrophils. In contrast, mast cells and TH_2 cells only promote tumorigenesis whereas NK cells only exhibit anti-tumor immunity [42]. Moreover, the major histocompatibility complex (MHC) system, cytokines, lymphocytes (B and T cells), and antigen-presenting cells (APCs) are also used by the host's adaptive immune

system to recognize and kill tumor cells with abnormal cell surface antigens. As a result, using a functional adaptive immune system to target mediators and inhibit immunological checkpoints is a strong cancer therapeutic technique. In the near future, further development of cancer vaccines and modified T-lymphocytes will be the most effective technique for treating cancer with fewer/no side effects [45] (Fig. 3).

Anticancer potentials of algae-derived metabolites

Microalgae anticancer potential

Microalgae are photosynthetic microorganisms that are categorized into prokaryotic (Cyanobacteria) and eukaryotic microalgae (diatoms, dinoflagellates, and coccolithophores). These phytoplanktons, which are found in practically all biomes (temperate to extreme) can be widely classified as fresh and marine water microalgae, providing up to 40% of global productivity [19]. These microalgae can be widely classified as autotrophic, heterotrophic, oligotrophic, and mixotrophic depending on their nutrient requirements [49]. Microalgae can be used to produce a wide range of bioactive compounds with various biotechnological purposes. They can be grown easily in photobioreactors and have quick generation times. Several factors influence the bioactive potential of microalgae, including species, growth phase, and culture conditions (temperature, nutrient availability, and light conditions). Although, due to its tremendous prominence in the field of biofuel production, microalgae's medical potential has been overlooked more than that of macroalgae [50]. Microalgae, in addition to marine bacteria and fungi, are ecologically important as producers and decomposers in the aquatic environment. Second, after food and biorefinery, their metabolic plasticity may stimulate therapeutic development to combat a diversity of diseases [51]. These algae have been shown to produce a variety of bioactive components (carotenoids, polysaccharides, and fatty acids) that have gained popularity due to their antimicrobial and antioxidant characteristics [19]. In recent eras, new therapeutic components can be developed and synthesized from natural resources by means of modern technology. Using the Discovery Studio 3.1 platform, the 3D models of the ligand ((9-Ethyliminomethyl-12-(morpholin-4-ylmethoxy)-5,8,13,16-tetraaza-hexacene-2,3-dicarboxylic acid) EMTAHDCA) obtained from cyanobacterium *Nostoc* sp. MGL001 were found to have a functional resemblance to existing drugs against 11 cancer-related proteins [52]. However, the in silico characterization of anticancer bioactive components from microalgae has only lately been addressed to a limited extent. Further, the microalgal compounds also have anti-inflammatory and immunomodulatory characteristics, making them a potential immunotherapeutic weapon against cancer. Sulfo-polysaccharides, PUFAs, sulfated lipids, and carotenoids (astaxanthin) are all microalgal immune-stimulatory components that drive

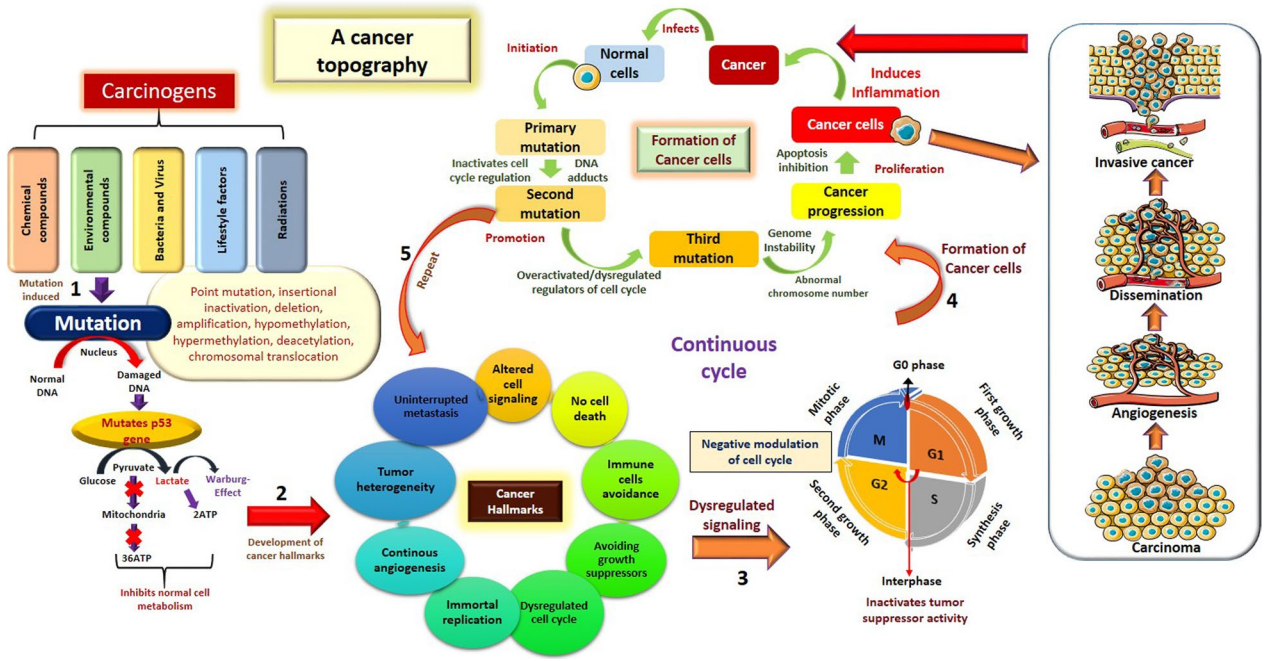

Fig. 3 Schematic representation of the molecular mechanism of cancer topography. Following a thorough analysis of the literature from articles, the figure is illustrated schematically and adapted [4, 18, 47, 48]

macrophage and dendritic cell proliferation and maturation. Apart from APCs, the dendritic cells often entitled "nature's adjuvant," are known to trigger cytotoxic T-lymphocytes, ultimately culminating in neoplastic cell death [53]. However, the current study indicates that microalgae might be a source of cancer treatments that work by promoting natural killer cells production, apoptosis-mediated cell death, cell cytotoxicity, and reducing tumor cells invasion either via a caspase-dependent or caspase-independent mechanism [19].

Microalgal carotenoids

Carotenoids from microalgae have been identified as a potential regime for treating inflammatory disease and cancer. *Chlorella* sp. (*Chlorella sorokiniana*, *Chlorella zoofingiensis*, *Chlorella vulgaris*, *Auxenochlorella prothecoides*, *Auxenochlorella pyrenoidosa*, *Chlorodium saccharophilum*, *Jaagichlorella luteoviridis*) is the major source of carotenoids followed by *Arthospira platensis* (cyanobacteria), *Dunaliella salina*, *Chlamydomonas reinhardtii*, *Tetraselmis suecica*, *Tetraselmis striata*, *Scenedesmus quadricauda, Dactylococcus dissociates, Asterarcys quadricellulare*, *Odontella aurita*, *Chlorobotrys regularis*, *Isochyrsis galbana*, *Chlorobotrys gloeothece, Nitzschia laevis, Chaetoceros neogracili, Munda aquilonaris, Phaeodactylum tricornutum, Porphyridium purpureum, Cantharellus cinnabarinus*, *Haematococcus lacustris*, etc. Carotenoids have been studied in vitro, in vivo, and in humans for their anti-inflammatory, anti-tumor, and anticancer activities [20, 54].β-carotene derived from *D. salina*, *C. reinhardtii*, *T. suecica*, *I. galbana* exhibit anticancer potentials against neuroblastoma, non-Hodgkin lymphoma, prostate, breast, liver, pancreatic, colorectal, and gastric cancer [54]. Among other microalgae that have been shown to kill prostate cancer cells by triggering apoptosis, *D. salina* is the main source of β-carotene [55]. Studies conducted in vitro indicate that β-carotene has been found to inhibit the Ku proteins, M2 macrophage polarization, and NF-κB activation [56]. Additionally, caveolin-1 protein expression, calcium/calmodulin-dependent protein kinase IV activity, the NF-κB/Akt pathway, the PI3K/Akt pathway, and the ERK pathway are all downregulated by β-carotene's antiproliferative activity, thereby arresting cell cycle and inducing apoptosis [54]. The inhibition of these signaling pathways has arrested the in vitro growth of distinct cancer cells/cell lines such as colorectal cancer cells (HT-29, Caco-2), hepatic cancer cells (HepG2, SK-Hep-1), colon cancer cells (HCT116), *H. pylori*-infected gastric cancer cells, esophageal carcinoma cells, adrenocorticotropic hormone-secreting pituitary adenoma cells (AtT-20) (further inhibiting cervical, breast, and hepatoma cancer cells), and lymphoblast cells (K562) apoptosis [54]. In in vivo murine model studies, β-carotene administration for a specific time period resulted in various anticancer actions. For example, β-carotene administration for 11 weeks suppresses M2 macrophage polarization thereby reducing colitis-associated colon malignancy [56]. Alongside, β-carotene's anticancer potential demonstrates DNA methylation, epigenetic modulation, and miRNA expression, all of which reduce the ability of colon cancer stem cells to proliferate and self-renew [57]. Oral treatment of β-carotene reduced the tumor weight of rat models suffering from liver cancer in hepatic cell lines (H22) [58]. In humans, β-carotene has been linked to the prevention of numerous malignancies due to its powerful antioxidant properties that reduce reactive oxygen species (ROS) formation, although further research is required to fully comprehend their potential [54].β-cryptoxanthin obtained from *P. trichornutum*, *A. pyrenoidosa*, *P. purpureum,* and *Cyanophora paradoxa* has been identified with antiproliferative, anti-migratory, and anticancer potentials. In vitro analysis has demonstrated suppressed migration, inhibition, and cell viability with increased apoptosis in the lung, colon (HCT116), and gastric cancer cells [54]. By causing caspase and cytochrome C mediated apoptosis as well as halting the cell cycle at the G0/G1 phase in a nude mouse xenograft, in vivo murine trials with β-cryptoxanthin treatment for 20 days have reduced angiogenesis and tumorigenesis of gastric cancer [59]. Furthermore, β-cryptoxanthin supplementation at 10 and 20 mg/kg inhibited tumor growth by downregulating sirtuin-1 (SIRT-1), retinoic acid receptor-β, and p53 [60], while 1 and 10 mg/kg treatment inhibited nicotinic acetylcholine receptor α7, both of which suppressed lung cancer in mice [61]. In human studies, β-cryptoxanthin reduced the risk of non-Hodgkin lymphoma, lung, breast, renal, head, and neck cancer [54]. Additionally, β-cryptoxanthin has been shown to cause apoptosis in human skin, lung, breast, and HeLa cancer cells and demonstrate cytotoxicity [20]. Further combination treatment with a chemotherapeutic drug (oxaliplatin) in colon cancer reduces the drug's toxicity [62].

Astaxanthin, a carotenoid with a potent antioxidant potential, shields cells from cyto- and genotoxicity brought on by ROS, epigenetic changes, cell cycle arrest in the G0/G1 or G2/M phase, activation of anti-apoptotic proteins, blocking angiogenesis and metastasis, and chromatin remodeling, ultimately enhancing tumor immunity [19, 63]. *Haematococcus pluvialis* is the predominant microalgal supplier of astaxanthin followed by *Tetraselmis* sp., *G. sulphuraria*, *Chlorococcum* sp., *C. sorokiniana*, and *C. Zofingiensi* [20]. This carotenoid induces several tumor suppressors (MAPK4, mapsin, breast cancer metastasis suppressor 1, and kail)

[64]. Apoptosis is triggered by stopping the cell cycle in a number of in vitro experiments on various cell lines. Astaxanthin induced cytotoxicity against ovarian cell lines by inhibiting NF-κB and stimulating apoptosis [65]. According to research, astaxanthin has the ability to decrease angiogenesis and metastasis in a variety of cell lines, including glioblastoma, murine hepatoma cells (H22), and adenocarcinoma gastric cell lines (AGS, KATO-III, MKN-45, and SNU-1). It also has the ability to control epigenetic changes [54]. In colon cancer, astaxanthin therapy was shown to downregulate Akt phosphorylation, cyclin D1, and Bcl-2 expression, as well as promote the production of p53, p21, p27, Bax, and caspase-3 [66]. Several dose-dependent in vivo applications of astaxanthin showed an anticancer effect on different malignancies such as gastrointestinal cancer (downregulates ERK-2, NF-κB, and cyclooxygenase (COX)-2; activates apoptosis), colon cancer (downregulates NF-κB and oxidative stress markers), oral cancer (downregulates Wnt/B-catenin and NF-κB signaling), esophageal cancer (downregulates NF-κB and COX-2), hepatic cancer (downregulates oxidative stress; upregulates serum adiponectin protein), skin cancer (downregulates tyrosinase activity), and lung metastatic myeloma (downregulates Bcl-2, ERK, and NF-κB; upregulates apoptosis) in murine models [54]. Moreover, astaxanthin is a good antioxidant agent that has been identified to elevate IL-6 and TNF-α in murine models prior to tumor initiation [67]. In human studies, astaxanthin is majorly evidenced to inhibit immune dysfunction alongside regulating the inflammatory response [68]. Additionally, the antiproliferative effect of carbendazim in MCF-7 cells in the G2/M phase is enhanced by the addition of astaxanthin [69]. Nevertheless, there is still a paucity of information on astaxanthin-related dose-dependent human cancer investigations.

Lutein obtained from *C. sorokiniana*, *C. zoofingiensis*, *A. protothecoides*, *D. salina*, *T. suecica*, and *C. reinhardtii* has demonstrated anticancer and anti-proliferative activity against non-Hodgkin lymphoma, renal cell carcinoma, hepatocellular carcinoma, pharyngeal, esophageal, neck, pancreatic, colon, bladder, and breast cancer [54]. According to in vitro studies in breast cancer lines (MCF-7 and MDA-MB-231), lutein inhibits transcription factor Nrf2 (including genes superoxide dismutase (SOD)-2 and HO-1), glycolysis, cell growth, and progression, as well as down-regulating NF-κB, pAkt, and pERK markers, inducing p53 signaling, transcription factor hairy and enhancer of split (HES)-1, and cellular apoptosis [70]. Other cell lines, including prostate cancer (PC)-3, sarcoma S180, lung cancer A549, colon adenocarcinoma, and leukemia cells, were also investigated to determine lutein's anticancer activity [54]. Lutein's anti-proliferation slows the progression of the cancer cell cycle by downregulating biomarker genes in prostate cancer and culminates breast cancer by upregulating pro-apoptotic genes and p53 signaling pathway inducing apoptosis alongside downregulating Bcl-2 genes further generating ROS [20]. In vivo studies reported lutein administration of 50 mg/Kg for 1 month alongside 4T1 cells injection, inhibiting breast cancer in murine models [71]. Similarly, 0.002% of dietary lutein downregulated cell proliferative proteins (β-catenin, K-ras, and Akt/protein kinase B) thereby reducing tumor formation [72]. Alongside the suppression of cytochrome P450 phase I enzyme in N-nitrosodiethylamine-stimulated hepatocellular carcinoma was also observed via lutein administration in murine models [73]. Further coadministration of lutein with doxorubicin exhibited higher inhibition of sarcoma S180 cells proliferation in mice [74]. The human dietary consumption of lutein has reduced the efficacy of different cancers which are discussed before in this topic.

Zeaxanthin is a xanthophyll mostly obtained from *Nannochloropsis oculata*, *Chloroidium saccharophilum*, and *Dunaliella* sp. with good anticancer potentials. Few in vitro, in vivo, and human investigations have examined the chemopreventive activity of zeaxanthin, despite its limited research [54]. This carotenoid has been identified to activate gastric cancer cell apoptosis by upregulating pro-apoptotic factors and MAPK signaling pathway alongside downregulating anti-apoptotic factors (Bcl-2) [75]. The anti-melanoma potential of zeaxanthin has also activated human uveal melanoma cells apoptosis by downregulating the melanoma cell-induced fibroblast migration and platelet-derived growth factor [54].

Many microalgae also contain the orange-colored marine xanthophyll molecule known as fucoxanthin such as *Chaetoceros neogracili*, *Isochrysis* sp., *Cylindrotheca closterium*, *Pleurochrysis carterae*, *Odontella aurita*, *Phaeodactylum tricornutum*, *Nitzschia laevis*, *Conticribra weissflogii*, *Tisochrysis lutea*, *Thalassiosira* sp., *Navicula* sp., *Amphora* sp., and *Pavlova* sp., OPMS 30543 [20, 54]. The anticarcinogenic characteristics of fucoxanthin include decreased tumor incidence, cancer cell inhibition, cell cycle arrest, induction of apoptosis, and controlled metastasis. Furthermore, Bcl-2 protein, caspase pathway (caspase-3, caspase-8, caspase-9), signaling pathways (MAPK, JAK/STAT, stress-activated protein kinases (SAPK)/JNK, and PI3K/Akt/mechanistic target of rapamycin (mTOR)), growth arrest and DNA-damage-inducible protein (growth arrest and DNA damage (GADD)45α), NF-B, CYP3A4 enzyme, connexin genes, expression of N-myc oncogene, angiogenesis, and survival are all involved in fucoxanthin-induced apoptosis. Alongside apoptosis, fucoxanthin also confers chromatin condensation, DNA laddering, and degradation [20, 76].

According to in vitro research, various cancer cell lines have shown fucoxanthin to have anticancer potential. Regarding gastric cancer, fucoxanthin suppresses myeloid cell leukemia 1 protein and cyclin B1 via JAK/STAT signaling pathway alongside the reduction in Bcl-2 thereby inducing autophagy and apoptosis by stimulating cleaved caspase-3, beclin-1, and microtubule-associated protein 1 light chain 3 [77, 78]. Similarly, fucoxanthin's anticancer properties reported beta-glucuronidase activity and NF-κB mediated pro-apoptotic activity in DLD-1 and HCT116 colorectal cancer cells, respectively [79, 80]. The further combined therapy of fucoxanthin with 5-fluorouracil exhibited a cytotoxic effect on both HCT116 and HT29 cell lines [81]. Alongside, the antiproliferative potential of fucoxanthin has been observed to downregulate the NF-κB pathway/expression in hepatic carcinoma (HepG2), Burkitt's and Hodgkin's lymphoma, and breast cancer (MCF-7 and MDA-MB-231) cells. Fucoxanthin's ability to kill human cervical cancer cell lines (HeLa) has also been linked to the downregulation of the Akt/mTOR pathway, PI3K/Akt, NF-κB, and a member of the histone cluster 1 H3 family [54]. Fucoxanthin has also been found to boost GADD45 expression in HepG2 and HTLV-1-infected T cells, causing G1 cell cycle arrest [82]. Regarding lung cancer, fucoxanthin has been identified to exhibit inhibitory effects by upregulating the pro-apoptotic p53 gene and Fas, alongside suppressing Bcl-2 [83]. Moreover, activation of different cell lines via mortalin (anti-apoptotic)-p53 binding can be suppressed via fucoxanthin application [84]. Regarding the central nervous system, fucoxanthin not only modulates the MAPK pathway but also downregulates PI3K/Akt/mTOR and p38 signaling pathway thereby stimulating ROS-triggered apoptosis by reducing invasion, angiogenesis, and cell proliferation. Based on in vivo studies, fucoxanthin has shown good chemopreventive potentials against colon cancer, lung cancer, hepatocellular carcinoma, cervical cancer, adenocellular carcinoma, and various tumor xenografts in various murine or rat models [54].

Violaxanthin, a compound isolated from *Dunaliella tertiolecta*, induces apoptosis in MCF-7 breast cancer cells without fragmenting DNA. Alongside, violaxanthin from *Chlorella ellipsoidea* exhibits apoptosis in colon cancer cells [20]. This carotenoid also results in the reversion of multi-drug resistance (MDR) in human MDR1 gene-transfected mice lymphoma cells (L1210) and human breast cancer cells (MDA-MB-231 and MCF-7) [51]. Furthermore, it has been demonstrated that violaxanthin from *Eustigmatos cf. polyphem* has radical scavenging activity [20].

Neoxanthin, being a xanthophyll carotenoid has been evidenced to upregulate cytotoxic effect upon treatment on HeLa and A549 cancer cells [51].

Siphonaxanthin, a keto-carotenoid obtained from *Codium fragile*, *Caulerpa lentillifera*, and *Umbraulva japonica*, has been evidenced with anticancer potential on various cancer [51]. Regarding the human leukemia cell line (HL-60), siphonaxanthin induces apoptosis by downregulating Bcl-2 expression. Simultaneously the condensation of chromatin, GADD45α, and apoptosis-inducing death receptor-5 (DR5) are upregulated [82]. Moreover, the anti-angiogenic effect of siphonaxanthin exhibits downregulated expression of mRNA, fibroblast growth factor receptor (FGFR)-1, early growth response (EGR)-1, and fibroblast growth factor (FGF)-1 [51].

Canthaxanthin is a keto-carotenoid primarily obtained from the mushroom *Cantharellus cinnabarinus*. Later, this carotenoid was also found in microalgae such as *Dactylococcys dissociates*, *H. pluvialis*, *Chlorella emersonii*, *C. zofingiensis*, *Coelastrella* sp., *Chlorococcum* sp., and cyanobacteria (*Aphanizomenon flos-aqua*, *Trichormus variabilis*, *Nodularia spumigena*, and *Anabaena* sp.). This carotenoid is known to exhibit anti-tumorigenic, chemopreventive, and antioxidant activity against human colon adenocarcinoma, melanoma cells, prostate cancer cells, and in vitro oral cancer [20].

Microalgal polysaccharides

Polysaccharides derived from microalgae are broadly classified as intracellular and extracellular (structural/cell-bound/cell wall) polysaccharides. The important parameters used in microalgae cultivation boost biomass productivity. Microalgae, on the other hand, produce fewer exopolysaccharides (EPS) than bacteria under normal growth conditions [85]. Furthermore, stress and limited nutrient availability have been shown to increase EPS content in microalgae. The primary EPS composition of microalgae includes polysaccharides, lipids, DNA, and proteins [86]. As a result, two-stage cultivation is required for efficient polysaccharide production. Although microalgae polysaccharides are mostly used for industrial purposes, their biostimulant characteristics have been related to anticancer properties [87]. Sulfate concentration and molecular weight affect polysaccharide potentiality. Therefore, the polysaccharides obtained from several microalgae/cyanobacteria are *Chlorella vulgaris*, *Chlorella pyrenoidosa*, *Arthospora platensis*, *Dixoniella grisea*, *Neochloris oleoabundans*, *Nostoc carneum*, *Porphyridium aerugineum*, *Dunaliella salina*, *Phaeodactylum tricornutum*, *Haematococcus pluvalis*, *Botryococcus braunii* UC 58, *Nostoc flageliforme*, *Rhodella violacea*, *Chlamydomonas reinhardtii*, *Anabaena* sp. 33,047, *Gloeocapsa* sp., *Graesiella* sp., *Spirulina* sp. LEB18 [85]. The sugar composition of these microalgae includes glucose, fructose, xylose, fucose, arabinose, rhamnose, mannose, galactose, maltose, and lactose. The inclusion of uronic

acids, pyruvates, and carbohydrate acyl groups thus gives EPS its anionic properties [88]. In contrast to macroalgae, microalgae have a lower proportion of sulfated and methylated polysaccharides. The partially purified EPS obtained from *C. pyrenoidosa* FACHB-9, *Scenedesmus* sp., and *Chlorococcum* sp. has been explored with radical scavenging generating abilities and anti-tumor activities (inhibiting cell viabilities and reducing colony count) upon treatment on HCT116 and HCT8 cell lines [89]. In vivo and in vitro studies using Graffi myeloid tumors, sarcoma S180 tumor cells, and breast cancer cells revealed additional anti-proliferative, anti-tumor, immunostimulatory, and cytotoxic characteristics of EPS produced from *Porphyridum cruentum* [90]. Simultaneously, nostoglycan, derived from the microalgae *Nostoc sphaeroids*, has been shown to enhance caspase-3-dependent apoptosis, limiting lung cancer cell proliferation while also protecting against ROS generation [91]. Moreover, dinoflagellate *Gymnodinium* sp. A3 EPS (GA3P (D-galactan sulfate, associated with L-(+)-lactic acid)) has been identified with both anticancer and enzyme inhibition (DNA topoisomerase I and II) activity [92]. Microalgae's polysaccharides have anticancer, antibacterial, and anti-adhesion capabilities that have been demonstrated to be crucial in the management of gastric carcinoma brought on by *H. pylori* [93]. Additionally, the anticancer and anti-proliferative properties of chrysolaminarin polysaccharides derived from the diatom *Synedra acus* have been demonstrated in HCT116 and DLD-1 cell lines [94]. Contrarily, despite a paucity of data and information, *Navicula* sp., *Tribonema* sp., and *P. cruentum* microalgal sulfated polysaccharides (SPs) have been investigated for anticancer potential in vivo and in vitro [20]. Nonetheless, the anticancer potentials of microalgal polysaccharides have received far less attention, with far fewer data available than for macroalgal polysaccharides.

Microalgal peptides

Therapeutic peptides, which are known to offer greater advantages than antibodies or proteins, have lately been explored in microalgae [45]. Enzymatically degraded microalgal byproducts produced from protein hydrolysates are the most common source of these bioactive peptides with unique amino acid residues. As a result, antiproliferative, antioxidant, and anti-microtubule action has been demonstrated on numerous cancer cell lines using these isolated therapeutic bioactive peptides [95]. Additionally, peptide-driven immune responses in cancer patients have produced previously unheard-of reactions. Microalgae hold great promise for the extraction of bioactive peptides for cancer treatment due to their accessibility and inexpensive cost [45]. However, only a few microalgae have been recognized as containing bioactive peptides exhibiting anticancer potential. Among all other microalgae, *Chlorella* sp. (*C. vulgaris, C. sorokiniana,* and *C. pyrenoidosa*) is mostly used for the production of bioactive peptides followed by *Dunaliella* sp. and *Pavlova lutheri* [45, 96]. Biologically active peptides extracted from *C. vulgaris* pepsin hydrolysate induced anti-proliferation and death of AGS cells after 24 h of exposure, arresting cell growth after the G1 phase. Additionally, antioxidant characterization showed that peptide-induced ROS generation is accountable for a number of harmful events in biological systems, including the attack on crucial biological components (DNA, protein, and lipid), and has been suggested as a prospective chemopreventive therapeutic for gastric carcinoma [97]. Human liver cancer cells (HepG2) were shown to be inhibited by enzymatic hydrolyzed derived polypeptides from *C. pyrenoidosa* by triggering apoptosis and necrotic death. The altered modifications, such as cell membrane shrinkage, nuclear condensation and disintegration, and the generation of black apoptotic bodies, were corroborated using phase-contrast microscopy [98]. Furthermore, malignant tumors gain the ability to spread by generating numerous metalloproteinases (MMP) that promote tumor migration and invasion, considering them potential targets for cancer treatment. Human fibrosarcoma (HT1080) cells are inhibited by bioactive peptides derived from *P. lutheri* via suppressing mRNA and MMP-9 expression [45, 99]. Tyrosinase activity can be decreased to lessen the risk of melanoma, which is brought on by UV radiation exposure that damages DNA. In mouse melanoma (B16F10) cells, bioactive peptides from *P. lutheri* have been shown to limit tyrosinase and melanogenesis activity, as well as reduced ROS generation, by boosting ERK phosphorylation [100]. Dolastatins derived from *Lyngbya* sp. and *Symploca* sp. has been shown to inhibit ovarian and cancer cell lines in humans. In addition, a dolastatin 10 derivative (TZT-1027) suppresses solid tumors (B-16 melanoma, colon 26 adenocarcinoma, M5076 sarcoma, and human cancer xenograft) in mouse models. Furthermore, although being less potent than dolastatin, auristatin PYE had better outcomes against colon cancer cells (DLD-1, HT 29, and COLO 205) [19]. Apart from dolstatins, grassypeptolide and curacin A are other bioactive peptides obtained from cyanobacterium *L. confervoides* and *L. majuscule*, respectively. Moreover, a wide variety of cyanobacterium-derived peptides (apratoxin (A-D, F), aurilides, coibamade A, lyngbyabellin (A, B, E, F, G, H, I, N), hoiamide (A-B), homodolstatin 16, largazole, obyanamide, majusculamide C, desmethoxymajusculamide, Palau amide, palmyramide, pitipeptolide (A and B), ulongapeptin, tasipeptin (A-B), veraguamide (A-G), wewak

peptin (A-D), nostocyclopeptide (A1-A2), symplocamide A, belamide A, etc.) have been investigated with anticancer potentials against different cancer cell lines [51]. However, only a few studies on the anticancer activities of microalgal peptides have been conducted, with positive results on six different cancer types [45]. Phycocyanin from cyanobacteria (*Arthospora platensis*) and red algae are phycobiliproteins that have been studied for their ability to stop cell cycle (G0/G1 or G2/M phase), reduce Bcl-2/Bax, COX-2, p-ERK, PEG2, CDK4, cyclin D1, NF-B, Fas, p53, ICAM-1, CD44, chromatin condensation, Cyt c release. By suppressing the Akt/mTOR/p70S6K pathways, phycocyanin also inhibits angiogenesis and metastasis while also inducing autophagy [101]. Furthermore, amino acid supplementation has been shown to reduce muscle protein breakdown while also suppressing inflammation. It has been discovered that microalgae contain glutamic acid in addition to 18 other amino acids. Along with glycine, *C. vulgaris* and *C. sorokiniana* have higher levels of alanine, valine, and leucine. Furthermore, antioxidant-active Mycosporine-like amino acids (MAA) are abundant in *Glenodinium foliaceum*, *Scenedesmus* sp., and *C. sorokiniana* [20].

Microalgal lipids

Microalgae lipids are classified into two types: polar (glycerophospholipids) and non-polar (triacylglycerols). Long-chain fatty acids combine with polar lipids to generate PUFAs, which are divided into three classes: Docosahexaenoic acid (DHA), Docosapentaenoic acid (DPA), and Eicosapentaenoic acid (EPA). Non-polar lipids, on the other hand, are primarily involved in energy conservation. Polar lipids are involved in the functioning of cellular signaling pathways in addition to maintaining structural integrity and membrane fluidity [102]. EPA and DHA are the omega (ω)-3 PUFAs obtained from *Porphyridium* sp., *Phaeodactylum* sp., *Nannochloropsis* sp., *Skeletonema* sp., *Thalassiosira* sp., *Cryptomonas* sp., *Tetraselmis* sp., *Heterocapsa niei*, *Isochrysis* sp., and *Chaetoceros* sp. [20]. DHA is the largest ω-3 (n-3) fatty acid among all PUFAs, and it has been demonstrated to have anti-tumor effects by triggering apoptosis via regulating the nucleus and mitochondria, culminating in lipid peroxidation (generating ROS) and cell cytotoxicity [19]. Alongside, PUFAs' anti-angiogenic characteristics aid in the generation of anti-metastatic activity in many malignancies. Moreover, PUFAs with a double bond location n-3 (EPA and DHA) have been investigated to confer better anticancer activity compared to PUFAs with n-6 (ω-6). Unlike unsaturated lipids, saturated lipids with shorter chain lengths (≤C10) are only known to demonstrate anti-tumor activity [103]. Multiple cancer cell lines, including breast cancer (MDA-MB-231, MCF-7, and KPL-1), prostate cancer, pancreatic cancer, and colon cancer (ACL-15 and HT-29), have been linked to dietary supplementation with n-3 PUFAs. In contrast, the anti-tumorigenic property of n-6 PUFAs has been disputed, as it has been shown in numerous human studies to promote carcinogenesis, which is inhibited when n-3 PUFAs are consumed [103, 104]. However, to date, inadequate data are available suggesting n-3 PUFA's anticancer potentials against skin carcinoma [105]. Alongside, atherosclerosis, increased pro-inflammatory eicosanoids/cytokines, cardiovascular and autoimmune diseases can all result from an excess of n-6 PUFAs consumption [104]. Additionally, DHA-mediated apoptosis is promoted in gastric cancer by activating JNK, ERK, and actuator protein (AP)-1, halting cell growth by increasing the levels of p53, Bax, and intracellular cytochrome c [106]. Among the n-3 PUFAs, DHA and EPA have been examined for their capacity to elicit cell cycle arrest in regard to ROS production, which downregulates death-regulating factors (Bcl-2) and releases mitochondrial cytochrome c to the cytoplasm, activating intrinsic pathway-induced caspase-dependent cytotoxicity [107, 108]. When cytochrome c is released as a result of stress-induced mitochondrial permeabilization, it activates caspase-3 by attaching to the N-terminal caspase-recruitment domain (CARD), which then activates caspase-9 by recruiting to the apoptosome, resulting in biochemical and cellular apoptosis [109]. Simultaneously, the interaction of n-3 and n-6 PUFAs alongside their molecular pathways in cancer therapy is still contentious and complicated, and there is a need for more research [104]. Anticancer medications are further modified by conjugating them with fatty acid molecules (such as doxorubicin conjugates, paclitaxel conjugates, cytarabine conjugates, gemcitabine conjugates, and ciprofloxacin conjugates), which boosts the efficacy of therapeutic selectivity against various cancer cells with lower doses [103]. In advanced breast cancer, a combination of ω-3 PUFAs, doxorubicin, cyclophosphamide, and fluorouracil chemotherapy, as well as mastectomy, inhibits proliferation and angiogenesis by downregulating Ki-67 and vascular endothelial growth factors (VEGF) expression. In addition, vitamin D supplementation decreases inflammatory markers (IL-1b, IL-6, IL-8, TNF-α) and tumor markers in colorectal malignancies. In cancer patients receiving chemotherapy, supplementing with ω-3 fatty acids reduces cancer-related fatigue [20]. Simultaneously, fluorouracil conjugated with DHA has been shown to be more efficient in treating gastric cancer [110]. Additional research and clinical studies (phases I–III) are needed, however, to ensure and define the biochemical processes and pharmacokinetics of these novel conjugates.

Polyunsaturated aldehydes (PUAs) are oxylipins produced by a variety of marine and freshwater diatoms when subjected to various environmental stresses. The abundance of various microbial (bacterial, virus, and plankton) communities have been hypothesized to be influenced by PUAs [111]. After cell disruption, PUAs are produced by oxidative degradation of PUFAs [112]. The diatoms that produce PUAs are mainly *Skeletonema costatum*, *Thalassiosira rotula*, *Skeletonema marinoi*, *Attheya longicornis*, *Chaetoceros socialis*, *Porosira glacialis*, *Chaetoceros furcellatus*, and *Pseudo-nitzschia delicatissima*. When grown in Conway's medium, Daigo IMK medium, Guillard's F/2 medium, or versions of both media, these diatoms/microalgae exhibit anticancer properties [5]. PUAs have been shown to have antiproliferative activity, reducing the sustainability of the human colon adenocarcinoma cell line (Caco-2) to 0% after 48 h of incubation at a concentration of 11-17 µg/mL. To validate the presence of apoptosis, the TUNEL assay was employed [113]. The cytotoxic potential of PUAs has also been established on cancer cells (lung (A549), colon (COLO 205), and adenocarcinoma cells, but not on healthy cells when incubated for 24 and 72 h [114].

On the other hand, few microalgae such as *Chlorella* sp., *Chlamydomonas* sp., *Scenedesmus* sp., *Ankistrodesmus* sp., *Nannochloropsis limnetica*, *Stephanodiscus hantzschii*, *Gomphonema parvulum*, *Cyclotella meneghiniana*, *Cryptomonas* sp., and *Monoraphidium* sp. have been evidenced for alternatively producing commercial sterols (β-sitosterol, stigmasterol, ergosterol, campesterol, and brassicasterol) [115, 116]. According to research, sterols have cytotoxic and anticancer properties. Furthermore, sterols suppress tumor growth, metastasis, and angiogenesis by inducing caspase-3-dependent apoptosis, Bax/Bcl2 increase, or blood cholesterol reduction, reducing the risk of cancer [20].

Other miscellaneous microalgal components

Vitamins, minerals, polyphenols, and Coenzyme Q, besides carotenoids, were demonstrated to possess strong anticancer properties [20]. Vitamin A obtained from various microalgae (*Tetraselmis suecica*, *Dunaliella tertiolecta*, *Chlorella stigrnatophora*, *Skeletonema costatum*, *Isochrysis galbana*, *Aphanizomenon flos-aquae*, *Tetradesmus Obliquus*, and *Spirulina* sp.) is composed of retinol, once in the body, it is metabolized into retinoic acid and retinoids [20, 117]. However, retinoic acid's activity is contradictory because it can activate the ERK pathway, which promotes angiogenesis and metastasis. In combination with other chemotherapeutic medicines and antioxidants, retinoic acid, on the other hand, prevents various cancer prognoses, enhancing the patient's survival rate [118]. Vitamin C is derived from various microalgae (*Nannochloropsis oculata*, *Nannochloris atomus*, *Chaetoceros muelleri*, *Pavlova lutheri*, *Rhodomonas salina*, *Skeletonema costatum*, etc.) and has been shown to have higher anticancer potential when administered intravenously rather than orally [119]. Cancer cells are sensitized and killed by vitamin C via a number of methods, including oxidative stress, immune cell stimulation, inflammation modulation, and signaling pathway interference [20]. Furthermore, vitamin C has been shown to cause protein modification and mitochondrial malfunction in cancer cells when it enters through sodium-dependent vit C transporter2 (SVCT2) and glucose transporters (GLUTs), respectively, boosting cancer cell mortality [120]. Furthermore, exposure to sunlight is the principal source of vitamin D, sometimes described as the "sunshine" vitamin. Microalgae, compared to terrestrial and aquatic plants and animals, have been found to synthesize more vitamin D when exposed to UVB. Several microalgae such as *Nannochloropsis oceanica*, *Skeletonema costatum*, *Pavlova lutheri*, *Isochrysis galbana*, and *Tetraselmis suecica* are excellent producers of vitamin D [20]. Although there is a lack of research and evidence on vitamin D from microalgae as an anticancer agent. However, fewer studies suggest that it has anticancer potential by interfering with gene expression and improving cancer patients' relapse-free survival [121, 122]. Among all other vitamins, marine microalgae (*Skeletonema costatum, Pavlova lutheri, Isochrysis galbana, Chlorella stigmatophora*, *Spirulina* sp., *Tetraselmis suecica*, and *Dunaliella tertiolecta*) is a good source of vitamin E. Supplementing with vitamin E (300–1000 mg/day) has been shown to reduce patient mortality [20, 123]. Vitamin E comes in eight different major isoforms (α, β, δ, γ-tocopherols and -tocotrienol). Vitamin E is frequently used to treat nephrotoxicity and ototoxicity brought on by the drug cisplatin [20]. Vitamin E (especially tocotrienol) has been found to have anticancer properties in addition to its neuroprotective ones, inhibiting cell proliferation, angiogenesis, and cell cycle arrest while simultaneously inducing autophagy, paratopsis, and apoptosis through various mechanisms involving the Bax/Bcl ratio, death receptor activation, and caspase-9 activations [20, 124]. There are two forms of vitamin K, sometimes known as "Koagulation vitamin": vitamin K1 (phylloquinone) and vitamin K2 (menaquinone). Vitamin K and its derivatives have been shown to have anticancer properties against a variety of malignancies. Several microalgae, including *Chlorella ellipsoidea*, *Tetraselmis suecica, Skeletonema costatum, Isochrysis galbana, and Pavlova lutheri* are good sources of vitamin K [20]. Furthermore, it has been demonstrated that vitamin K activates p21 and CDK1 inhibitors through a number of

methods, killing cancer cells, including upregulation (Fas/FasL, NF-kB, and p53) and downregulation (Bcl-2/Bcl-xl and Bax/Bak) of numerous factors, as well as caspase-3 activation pathways [125].

Marine microalgae (*Tetraselmis chuii*, *Botryococcus braunii*, *Phaeodactylum tricornutum*, *Chlorella* sp., and *Spirulina* sp.) are high in macrominerals and microminerals, both of which have been shown to have antioxidant properties, lowering cancer risk [20]. Further antioxidant multivitamin and mineral (AMM) supplementation reduces oxidative damage caused by chemotherapy and radiotherapy in cancer patients, restoring endogenous and exogenous antioxidants and trace elements [126].

Microalgae (*Diacronema lutheri*, *Phaeodactylum tricornutum*, *Haematococcus pluvialis*, *Chlorella vulgaris*, and *Tetraselmis suecica*) produce polyphenols and their derivatives (phenols, flavonoids, dihydrochalcones, and proanthocyanidins). Researchers have discovered that polyphenols have anticancer and antioxidant capabilities [20, 127]. Certain cancers are inhibited from proliferating by the antioxidant characteristics of polyphenols (phenols and flavonoids), which elevate radical scavenging capability [128]. By activating pro-apoptotic, antiproliferative, and anti-metastatic pathways, polyphenols (genistein, quercetin, and ellagic acid) have been demonstrated to alter molecular targets, suggesting their anticancer potential [20].

Ubiquinone, often known as coenzyme Q (CoQ10), is a well-known inducer of mitochondrial oxidative phosphorylation and adenosine triphosphate (ATP) production [129]. Few microalgae (*Porphyridium purpureum, Chlorella pyrenoidosa*, and *Isochrysis galbana*) have been shown to produce more CoQ10, either naturally or when freeze-dried. CoQ10 and Alpha-Lipoic acid (ALA) combination therapy has been shown to reduce inflammation and cancer risk by considerably enhancing antioxidant activity. Nonetheless, a higher risk of cancer has also been connected to low ubiquinone levels [20] (Table 1).

Macroalgae anticancer potential

Marine macroalgae are a substantial source of bioactive substances including polysaccharides, lipids, and proteins (primary metabolites) as well as phenolic compounds, halogenated compounds, sterols, terpenes, and short peptides (secondary metabolites) [144]. Based on their morphology and pigmentation, macroalgae are divided into three groups: green (Chlorophyta), red (Rhodophyta), and brown (Phaeophyta) [21]. Several biological properties of macroalgae have been considered notably anti-diabetic, anti-inflammatory, anticancer, antimicrobial, antihypertensive, anti-viral, neuroprotective, and fat-lowering activities [144]. The biological properties of the macroalgae-derived bioactive compounds depend on their extraction process which is available in detail in [21].

Macroalgal polysaccharides

SPs are anionic polymers biosynthesized by macroalgae as an important component of their cell walls and are regarded to be vital for physiological adaptation to the high ionic strength of the marine environment. The SPs that are widely used as potential bioactive compounds include ulvans, galactans (agarans and carrageenans), and fucoidans from green, red, and brown macroalgae, respectively [145]. In terms of anticancer activity, SP with low molecular weight and high sulfate content is considered advantageous [1]. The sulfate groups are covalently bonded in varying quantities (0 to 41%) to the carbohydrate atoms via ether bonds [146].

Ulvan is a polysaccharide of green macroalgae derived from various genera of *Ulva*, *Caulerpa*, *Monostroma*, *Codium*, and others. The structure of ulvan consists of xylose, rhamnose, uronic acids (glucuronic and iduronic acid), sulfate groups, and trace amounts of mannose, and galactose. Both D-glucuronosyl-(1,4)-L-rhamnose 3-sulfate and L-iduronic acid-(1,4)-L-rhamnose 3-sulfate are repeating disaccharide units that constitute the compound; sulfate content (18.9%) with molecular weights ranging between 1.8×10^5–2×10^6 [147]. Ulvan's interaction with the Toll-like receptor (TLR)4 receptor leads to the P13K/Akt and NF-κB signaling pathways to be activated, which causes the expression of IL-8, TNF-, and CCL20 to be induced to prevent tumor growth [148]. In a study using the human hepatoma (HepG2) cell line, ulvan administration triggered apoptosis by activating the caspases-mediated mitochondrial signaling system that produced cytochrome c (Cyt c), activated caspase-3, − 9, and Bax-Bcl-2 ratio [149].

Carrageenan is mainly composed of a linear chain of alternating α-1,3- and β-1,4-glycosidic linkages connecting 3-linked β-D-galactopyranose units and 4-linked 3, 6-anhydro-α-galactopyranose [10, 150] and are extracted from *Kappaphycus alvarezii*, *Eucheuma denticulatum*, *Chondrus crispus*, *Chondrus pinnulatus*, *Chondrus armatus*, *Chondrus yendoi* [10, 146]. The molecular mass of carrageenan range from 500 to 1000 kDa. According to their sulfate content and position, carrageenans can be divided into six categories: kappa (κ-), mu (μ-), iota (ι-), beta (β-), lambda (λ-), theta (θ), and nu (ν-) carrageenan. Among them, the most important types are κ-, ι-, and λ-carrageenans with 20%, 33%, and 41% of sulfate content, respectively [146]. In the signaling pathway for Wnt/β-catenin, Wnt interacts with the Frizzleds (Fr) receptors and coreceptors like low-density lipoprotein receptors (LPR5/6) activating the dishevelled (Dvl) protein. It destabilizes the destructing complex (Wnt/Fr/LRP/

Table 1 List of compounds with anticancer properties derived from various microalgae

Microalgae	Compounds	Models (in vivo/in vitro)	Mode of action	References
Isochrysis galbana and *Nannochloropsis oculata*	Exopolysaccharide	HeLa cells	Antioxidant capacity and antiproliferative activity	[130]
Chaetoceros calcitrans	Ethanolic extract (absolute)	Breast adenocarcinoma (MCF-7), breast epithelial (MCF-10A), peripheral blood mononuclear cells (PMBC)	Stimulation of pro-apoptotic protein (Bax and caspases 3) and 7 transcripts; apoptotic protein formation	[131]
Amphidinium carterae, *Amphidinium operculatum*, *Prorocentrum rhathymum*, *Heterocapsa psammophila*, *Coolia malayensis*, *Ostreopsis ovate*, *Symbiodinium* sp.	Methanolic Extract (80%)	Murine macrophage cell line (RAW 264.7) and human promyelocytic leukemia cell line (HL-60)	Cell viability reduction and cytotoxic effect	[132]
Skeletonema marinoi, *Alexandrium tamutum*, *Alexandrium minutum*, *Alexandrium andersoni*	Hydrophobic fraction (acetone (1): water (1))	Melanoma cancer cell line (A2058) and normal lung fibroblast (MRC-5)	Cell viability reduction and cytotoxic effect in both cells	[133]
Chlorella sorokiniana	Aqueous extract (hot water)	Lung adenocarcinoma cell lines (A549 and CL1-5)	Bax/Bcl-2 ratio, caspase-9, caspase-3 and poly(ADP-ribose) polymerase (PARP) activation; apoptosis induction	[134]
Thalassiosira rotula, *Skeletonema costatum*, *Pseudo-nitzschia delicatissima*	Polyunsaturated Aldehydes (PUAs)	Human colon adenocarcinoma cell line (Caco-2)	Reduced cell viability; DNA fragmentation; apoptosis induction	[113]
Dunaliella tertiolecta	Violaxanthin	Breast adenocarcinoma (MCF-7), human epithelial breast cancer cell (MDA-MB-231), lung adenocarcinoma cell line (A549), and human prostate adenocarcinoma cells (LNCaP)	Reduced cell viability; cytotoxic effect; apoptosis induction; no DNA fragmentation	[135]
Navicula incerta	Stigmasterol	Human liver cancer cell line (HepG2)	Cytotoxic effect; apoptosis induction	[136]
Conticribra weissflogii	Fucoxanthin	Sepsis mouse model	Inhibition of NF-κB signaling pathway; anti-inflammatory; reduced interleukins (IL-1β and IL-6) and tumor necrosis factor (TNF)-α expression	[137]
Porphyridium purpureum	Zeaxanthin	Melanoma cells (A2058)	Antiproliferative activity; chromatin condensation; nuclear blebbing; inhibition of NF-κB signaling pathway; upregulation of pro-apoptotic factors (Bim and Bid); apoptosis induction	[138]
Nannochloropsis oculata	Sterols	Human promyelocytic leukemia cell line (HL-60), colorectal carcinoma cell line (HCT-116), adenocarcinoma human alveolar basal epithelial cell line (A549), human colon adenocarcinoma cell line (SW-480), hepatocellular carcinoma cell line (Hep3B)	Anti-inflammatory and apoptosis induction	[139]
Spirulina maxima	Sterols	Breast adenocarcinoma (MCF-7)	Cytotoxic effect	[140]
Tetradesmus obliquus	Peptide	-	Antioxidant and angiotensin-converting-enzyme (ACE) inhibitory activities	[141]
Dunaliella salina	β-carotene	Human prostate cancer cell line (PC-3)	DNA fragmentation; mitochondrial dysfunction; apoptosis induction	[55]

Table 1 (continued)

Microalgae	Compounds	Models (in vivo/in vitro)	Mode of action	References
Haematococcus pluvialis	Astaxanthin	Human hepatoma cancer cell line (HepG2)	Glutathione depletion; cell cycle arrest (G0/G1 phase); DNA fragmentation; apoptosis induction	[142]
Phaeodactylum tricornutum	Sulfated polysaccharides	Human hepatoma cancer cell line (HepG2)	Apoptosis induction	[143]

Dvl/Axin), thus accumulating β-catenin. This pathway is considered crucial for the formation of cancer stem cells [146, 151]. The application of carrageenan on different cell lines has both the pro-tumor and anti-tumor activity of Wnts in line with the type of tumor and the Wnt ligand involved. Contradictory results on Wnt-cascade signaling have noted the tumor-suppressing efficacy against leukemias, neuroblastoma, thyroid cancer, melanoma, and ductal breast cancer as well as tumor-promoting activity against gastric, prostate, pancreatic, melanoma skin, and non-small cell pulmonary cancer [151].

Fucoidan obtained from brown macroalgae (*Ascophyllum nodosum*, *Ecklonia cava*, *Undaria pinnatifida*, *Fucus vesiculosus*, *Sargasssum hemiphyllum*) [152] have molecular mass categorized into three groups: high molecular mass (> 10,000 kDa), intermediate molecular mass (10–10,000 kDa), and low molecular mass (< 10 kDa). It is composed of a backbone of 3-linked α-L-fucopyranose units or alternating 3-linked α-L-fucopyranose and 4-linked α- L-fucopyranose units, along with traces of glucose, mannose, xylose, galactose, rhamnose [152, 153]. Oversulfation of fucoidans promotes their bioactivity and is found to be a strong inhibitor of angiogenesis. The interaction of fucoidan with several cancer-related pathways makes it a multipotent compound. It inhibits the phosphorylation of phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT), mTOR while decreases the level of MMP-2 and MMP-9 on different cancer cell lines [153]. P13K/AKT signaling regulates the pro-apoptotic Bcl-2 subunits, which cause Cyt c to be released from the mitochondria and activate the caspase pathway [154]. In an in vitro investigation by Cho et al. [155], fucoidan has been shown to reduce NF-κB activity on bladder carcinoma cell lines. The same study revealed that fucoidan treatment induced the level of p21WAF1, a cell cycle inhibitor, through upregulation of Akt signaling pathway. Fucoidan has shown promising results against various carcinoma cell lines including acute myeloid leukemia (NB4, HL-60), colon, breast, lung, uterine, ovarian, endometrial, and colorectal cancer [153]. In the MAPK/ERK pathway, the protein level of the phosphorylated ERK1/2 is reduced by fucoidan for apoptotic induction. However, both the inhibitory and stimulatory expression of p38 MAPK has an anti-proliferative effect on colon, leukemia, and gastric cancer cells [153]. Fucoidan's anticancer effects are also linked to its capacity to obstruct a plethora of growth-related receptors, including the estrogen receptor, TGF-β, bone morphogenetic proteins (BMPs), and VEGFs (ER) [156–159].

Macroalgal peptides

Peptides with anticancer properties are low molecular weight cationic peptides. In comparison to conventional chemotherapy, anticancer peptides are known to efficiently inhibit tumor growth, migration, and angiogenesis. Several mechanisms of anticancer peptides are involved in inhibiting tumorogenic activities including cell membrane destruction, apoptosis, inhibition of tumor angiogenesis, and immune regulation [160]. A study of papain- and pepsin-digested hydrolysates obtained from *Pyropia haitanensis* showed anti-proliferative activity against breast (MCF-7), liver (HepG2), and lung (A549) carcinoma cell lines. They exhibited an IC_{50} value ranging between 59.09 to 272.67 μg/ml. In addition, a novel peptide (QTDDNHSNVLWAGFSR) was isolated with an inhibitory effect of 61.36% (at 500 μg/ml) on the HepG2 cancer cell line [161]. Another study by Fan X et al. [162] showed that polypeptides isolated from *Porphyra haitanensis* exhibited anti-proliferative activity against A549, HepG2, HT-29, MCF-7, SGC-7901 cancer cell lines with an IC_{50} value within 191.61 and 316.95 μg/ml. Furthermore, two novel peptides (VPGTPKNLDSPR and MPAPSCALPRSVVPPR) showed anti-proliferative activity against MCF-7 (IC_{50} = 200.97 μg/ml) and HepG2 (IC_{50} = 276.85 μg/ml). By halting the cell cycle at the G_0/G_1 phase and causing apoptotic cell death, polypeptides exerted an anticancer action on cancer cells. *Undaria pinnatifida* is a green macroalgae that is rich in proteins and has remarkable bioactive qualities; however, there is little evidence of its anticancer potential [163]. In an investigation by Rafiquzzaman [164], glycoprotein isolated from *Undaria pinnatifida* functions as a natural, bioavailable antioxidant with DNA-protective properties. Because molecular weight and structural properties govern the migration and penetration of peptides inside the body, the low molecular weight hydrolysates of protein and peptides of *U. pinnatifida* are likely to exhibit high radical scavenging action [163].

Macroalgal lipids

PUFAs, which contain ω-6 and ω-3 fatty acids, are crucial for maintaining various metabolic processes that lower the risk of heart disease, cancer, and inflammatory diseases. ω-6 fatty acids are the linoleic and arachidonic (AA) acids and ω-3 fatty acids are EPA and DHA [165]. The short-chain PUFAs are the ω-3 alpha-linolenic acid (ALA), and ω-6 linoleic acid (LA), while the long-chain PUFAs are the ω-3 EPA and DHA, and ω-6 AA [166]. Mammals lack the enzymes essential for the synthesis of PUFAs and hence have to be obtained through diet. The dietary ratio of ω-6:ω-3 has to be 2:1 in healthy individuals; however, excessive intake of ω-6 can lead to diseases like cancer [165, 167]. Epidemiological evidence on the association between PUFA and cancer indicates that ω-3 PUFA prevents cancer whereas ω-6 PUFA induces it [167]. Macroalgae possess an abundant amount of

long-chain PUFAs acting as a good source with nutritional value. In comparison to green and red macroalgae, brown macroalgae contain the highest quantity of PUFAs [168, 169]. The potential sources of PUFAs from macroalgae are *Gracilaria corticata*, *Gelidium* sp., *Pyropia* sp., *Undaria pinnatifida*, *Ulva*, *Gelidiella* sp., *Polysiphonia* sp., *Monostroma*, *Caulerpa*, *Rhodymenia sonderi*, *Acanthophora* sp., *Acrosiphonia*, *Bryopsis*, *Cryptonemia undulata*, *Halymenia* sp., and *Udotea* [170]. PUFA from *Adenocystis utricularis* displayed growth inhibition of human breast tumor cells (MCF-7 and MDA-MB-231) between 61.04% and 69.78%. The cell viability for MCF-7 (68.7%) and MDA-MB-231 (89%) reduced on exposure to fatty acids from *Adenocystis utricularis* for 72 h. Furthermore, the 100 µg/ml concentration of fatty acids had > 50% anti-proliferative effect against breast tumor cell lines [171]. *Fucus spiralis* fatty acid-containing petroleum-ether fraction was cytotoxic to the HeLa cell line due to its anti-migratory, anti-angiogenic, and cell cycle-arresting effects. Its IC_{50} value was 43.74 µg/ml [172]. Sterols, belonging to a subset of steroids, are the amphipathic lipids with a hydroxyl group (C3 carbon atom) and a branching chain (C17 carbon atom). Many types of sterols such as cholesterol, clionasterol, isofucosterol, fucosterol, sargasterol, and others are found in macroalgae several biological properties [173]. According to Li et al. [174], saringosterol acetate from *Sargassum fusiformis* had anti-proliferative action on the MCF-7 cell line via inducing mitochondrial-mediated apoptosis (IC_{50} = 63.16 µg/ml). Commercially purchased fucosterol induced mitochondrial-mediated apoptosis, endoplasmic reticulum stress, and anti-angiogenic effects on human ovarian tumor cell lines (ES2 and OV90) with an IC_{50} value of 62.4 µM (ES2) and 51.4 µM (OV90) [175].

Macroalgal vitamins

Vitamins are necessary to keep the body's physiological and biochemical processes functioning properly. It has been reported that several macroalgae possess vitamins beneficial for preventing various diseases. Vitamin B_{12} is known to exist in the highest proportion in red algae (*Porphyra* sp.). Other species of macroalgae with vitamin B_{12} are *Palmaria longat*, *Porphyra tenera*, *Enteromorpha*, etc. All species of green, red, and brown macroalgae possess vitamin C and vitamin E (α-tocopherol) including *Undaria pinnatifida* and *Laminaria digitata* which have both the vitamins [176]. Vitamin A as already described above have anticancer property. By suppressing the expression of myosin light chain kinase via the MAPK pathway, Zuo et al. [177] found that All-trans retinoic acid (ATRA) has an antimigratory effect against human colorectal carcinoma cells (RKO). B vitamins (B_1, B_2, B_3, B_5, B_6, B_7, B_9, B_{12}) are important for generating cofactors required for important cellular and metabolic functions [178]. Vitamin B_1 (thiamine) (2 µg/ml) inhibited the proliferation of the MCF-7 breast carcinoma cell line by 63% [179]. Vitamin B_6 comprises pyridoxal, pyridoxine, pyridoxamine, along with their phosphorylated forms: pyridoxal-5'-phosphate, pyridoxine-5'-phosphate, pyridoxamine-5'-phosphate [178]. The strong anti-inhibitory activity was observed at a concentration of 20 µM pyridoxal against B16F10 murine melanoma cells [180]. In an in vivo experiment, supplementation of folate and vitamin B_{12} to azoxymethane-induced carcinogenic mice combats against the cytotoxicity and oxidative stress of azoxymethane [181]. Based on the administration route mentioned above, Vitamin C, often known as ascorbic acid, exhibits anticancer effects. Hepatocellular tumor cells (Hep3B) were treated with low-dose methotrexate and vitamin C in combination to induce H_2O_2 production and activate caspase-8/-9, hence promoting cell death [182]. The proliferation of the anaplastic thyroid carcinoma cell lines (8505C and C643) was inhibited successfully on treatment with vitamin C at a concentration of 1 mM through ferroptosis via GPX4/PTGS2 pathway [183]. Our skin on exposure to sunlight (UVB, 290–320 nm) produces vitamin D, a seco-steroidal prohormone. It goes through metabolic processes in the liver and kidney to yield calcitriol (biologically active metabolite). Apart from its role in bone metabolism, it is reported to function in cancer treatment and prevention [184]. In a recent study on breast cancer cell lines (MCF-7 and MDA-MB-231), the reduction in the cell viability was 72% (10 µM vitD) at 24 h for MCF-7. This was due to the imbalance in cellular iron homeostasis inducing oxidative stress contributing to cell death [185]. Also, a study by Casadei-Gardini et al. [186] evaluated patients with cholangiocarcinoma undergoing surgery for disease-free survival (DFS) and found that intake of vitamin D improves DFS. Vitamin E and Vitamin K have already been described above and show anticancer activity. α-tocopherol (Vitamin E) exhibits anti-tumor activity on squamous carcinoma cell (ORL-48) at IC_{50} value of 2.5 µg/ml through apoptotic cell death and sub-G_0 phase cell cycle arrest [187]. A recent study on vitamin K_2 depicted AMPK-dependent autophagic cell death in human bladder tumor cells (T24, EJ, and J82) on induction of PI3K/AKT/hypoxia-inducible factor-1α (HIF-1α)-mediated glycolysis [188]. Most of the vitamins have shown controversial results on cancer and further investigation needs to be performed for analyzing their exact roles.

Other miscellaneous macroalgal components

Carotenoids are a macroalgal pigment that includes fucoxanthin, β-carotene, astaxanthin, violaxanthin,

capsanthin, siphonaxanthin, lutein, neoxanthin, and others [189]. Among them, the major carotenoids are the fucoxanthin widely distributed in brown algae (*Undaria pinnatifida*, *Laminaria japonica*, etc.). The structure of fucoxanthin possesses an allenic bond, a 5,6-monoepoxide, and an acetylated group [190]. With regard to anticancer activity, fucoxanthin, and fucoxanthinol (metabolite) induce apoptotic cell death, cell cycle arrest, antiproliferation, and anti-angiogenic effect [189]. Fucoxanthin exhibits its effect by downregulating MAPK, Bcl-2, MMP-9, and mRNA expression levels of CD44, CXCR4 and stimulation of poly-ADP-ribose polymerase (PARP), and caspase-3,-8,-9 [1]. An analysis by Wang et al. [191] showed that the human bladder cancer T24 cell line was inhibited by fucoxanthin at a concentration of 5 μM and 10 μM via G_0/G_1 cell cycle arrest through downregulation of CDK-2, CDK-4, cyclin D1, cyclin E, and upregulation of p21, CDK-inhibitory protein. Fucoxanthin was also responsible for the downregulation of the mortalin-p53 complex. On treating with *Undaria pinnatifida*-derived fucoxanthin, the growth of MDA-MB-31 (human breast cancer) and tumor-induced lymphangiogenesis were suppressed by reducing the concentrations of VEGF-C, phospho-AKT, VEGF receptor-3, phospho-P13K, NF-κB in human lymphatic endothelial cells. However, in *in vivo* MDA-MB-31 nude mouse model micro-lymphatic vascular density (micro-LVD) was reduced [192].

Polyphenols are produced by seaweeds to boost their antioxidant properties and act as radical scavengers. They produce polyphenolic compounds including phlorotannins, flavonoids, bromophenols, mycosporin-like amino acids, and phenolic terpenoids [1]. Phlorotannins are the major polyphenols unique to brown algae [20] such as kelps, rockweeds, *Ecklonia cava*, *Laminaria japonica*, and *Sargassacean* sp. and comprise a monomeric unit phloroglucinol (1,3,5-trihydroxybenzene) [1]. On the basis of the links between the monomeric units, phlorotannins are divided into four classes: phlorethols and fuhalols (ether links), fucols (phenyl links), fucophlorethols (ether and phenyl links), and eckols and carmalols (dibenzodioxin links) [193]. Zenthoefer et al. [194] produced an acetonic extract of *Fucus vesiculosus* (thallus) for inhibiting the viability of pancreatic cancer cells (Panc89 and PancTu1). The EC_{50} value for Panc89 was 71.47 μg/ml and PancTu1 was 76.96 μg/ml. Also, the inhibitory rate of Panc89 and PancTu1 was 80.3% and 82.6%, respectively. The application of phlorethols from *Costaria costata* showed an IC_{50} value of 92 μg/ml, 94 μg/ml, 96 μg/ml, and 102 μg/ml for HT-29, HCT-116, MCF-7, and SK-MEL-28, respectively [193]. Eckol prohibited Reg3A-induced SW1990 cells from multiplying (pancreatic human cells) [195], while dieckol had anti-proliferative and anti-migratory impact on non-small-cell pulmonary cancer by regulating PI3K/AKT pathway [196].

Similar to microalgae, many macroalgae-derived components have also been investigated using in silico methods, albeit with very scanty data. Although caulerpin from *Caulerpa racemosa* was molecularly docked, it showed that it was an efficient ligand but had a reduced total binding energy when considering whether it could be used as a therapeutic molecule [197]. Simultaneously, another study of the anticancer activity of metabolites from *Caulerpa* sp. has been identified as an effective ligand against glucose 6-phosphate dehydrogenase (G6PDH) and 6-phosphogluconate dehydrogenase (6PGD) for targeting the pentose phosphate pathway in colorectal cancer treatment [198] (Fig. 4, Table 2).

Can multi-drug-resistant gastric cancer be effectively treated with algal metabolites?

Antimicrobial resistance has rendered many conventional antibiotics ineffective in a number of people with *H. pylori* infection [245]. Antimicrobial resistance to metronidazole, tetracycline, quinolones, clarithromycin, and rifabutin has emerged as a result of gene modulations or mutations, according to molecular investigations [246, 247]. *H. pylori* has been classified as priority 2 by the World Health Organization (WHO) due to antibiotic resistance, despite the fact that it is found colonizing in 50% of the human stomach [248]. As a result, a method to lower cancer's morbidity and mortality has been found in algae with special metabolites that can stop the progression of an *H. pylori* infection into gastric cancer in the era of multi-drug resistance [247]. However, there is a scarcity of data on the antibacterial activity of microalgal bioactive components (mostly carotenoids) against *H. pylori*. In macroalgae, fucoidan is widely used for its anti-*H. pylori* activity. Infection with *H. pylori* raises the risk of gastric and colon cancer. Gastric cancer (GC) arises from a complicated, multi-step process that starts with normal mucosa and progresses to non-atrophic gastritis. In a cascade, the progression of superficial gastritis to atrophic gastritis leads to the production of metaplasia, dysplasia, and intestinal-type cancer [249]. The expression of several outer membrane proteins/adhesins by the bacteria (BabA, SabA, AlpA/B, HopZ, and OipA) aids in the establishment of an intimate relationship with the gastric mucosa cells of the host. Alongside adhesins, numerous virulence factors (vacuolating cytotoxin A (VacA), cytotoxin-associated gene A (CagA), and urease) produced by *H. pylori* are integrated into host cells via the type 4 secretory system (T4SS) within cag pathogenicity island (cag PAI) for initiating pathogenesis [249, 250]. Instead of using bactericidal drugs, antiadhesives can prevent the pathogenesis that results from *H. pylori*

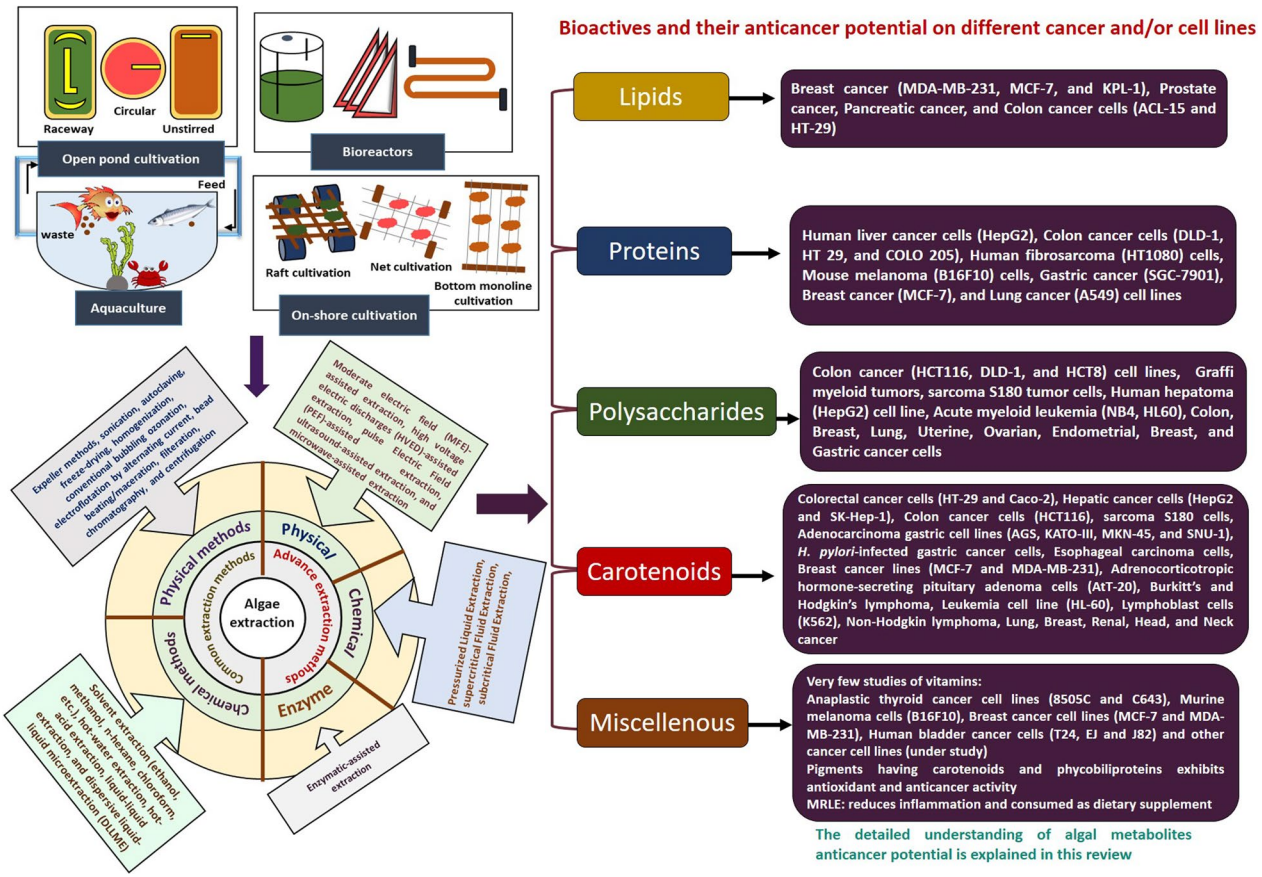

Fig. 4 Different algal growth and extraction methodologies for bioactive components, as well as their potential applicability to various cancers and cell lines

adhering to stomach mucus via lectin-like molecules. In microalgae, *Chlorella* sp. and *Spirulina* sp. can be exploited cost-effectively for their polysaccharides have been evidenced to favor anti-adhesive action in the gastric environment reducing > 90% *H. pylori* load observed in BALB/c mice models [251]. These algal polysaccharides have not been shown to impede in vitro bacterial growth, but they can prevent *H. pylori* infection/reinfection due to their anti-adhesive characteristics, making them a safe and cost-effective option [252]. In silico analysis of algal peptide interaction with *H. pylori* suggested peptides from green microalgae *Tetradesmus* sp. have been found active inhibitors against three virulent factors (Cag A, VacA, and Htr A) of *H. pylori* [253]. Additional probiotic therapy utilizing the carrageenan-encapsulated *Lactobacillus fermentum* UCO-979C strain has demonstrated anti-*H. pylori* efficacy under fasting conditions (pH 3.0) [248]. Although about 2% to 3% of people develop gastric cancer, this is primarily owing to the infection's persistence. Biofilm development, in addition to mutation, enhances bacterial antibiotic resistance. Considering algae's powerful predator defense mechanisms, bioactive substances identified in them are among the most promising sources. Algal extracts have also been shown to degrade the biofilm polymer matrix, resulting in an anti-film effect that, when coupled with antibiotics, prevents bacterial colonization from progressing and developing into gastric cancer [254]. In addition to genetic and environmental factors, modifications to the stomach adaptive system result in endoplasmic reticulum (ER) stress, which activates the unfolded protein response and causes precancerous lesions to form at the precancerous stage [255]. Because pro-apoptotic proteins (Bim and Bax) are present while VacA interference is present, ER stress causes CHOP transcription, which speeds up apoptosis. Activation of NF-κB, on the other hand, inhibits apoptosis via A20 deubiquitinylase activity, resulting in infection-mediated GC that persists [249, 256]. Furthermore, the increase in autophagosomes as a result of autophagy activation/inhibition enhances invasion and metastasis by causing ROS-mediated oxidative stress in the early stages of cancer. The autophagy generated by VacA exposure has been shown to be contradictory; nevertheless, autophagy

Table 2 List of compounds with anticancer properties derived from various macroalgae

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Green seaweeds										
Caulerpa racemosa Ulva lactuca	Seaweed hydrolysates extracted by subcritical water extraction	Phenolic and flavonoids	Abelson leukemia virus infected BALB/c mice macrophage	RAW 264.7	In vitro	Antioxidant	ROS scavenging ability	Total antioxidant = 8.03 mg/g Total antioxidant = 11.82 mg/g	50 µg/ml	[199]
Caulerpa racemosa var. macrophysa	Methanol extract	Phenolic and flavonoids	Hepatoma Human cervical adenocarcinoma	Huh-7 HeLa	In vitro	Anti-proliferative and ROS production	Downregulation of the *CDC2* gene and upregulation of *BAX* occurred in both the cell lines. However, *Cas-3* was upregulated only in Huh-7 and *p53* gene was induced in HeLa only	ROS inhibition (42%) ROS inhibition (56%)	EC_{50} = 23 µg/ml (24 h) EC_{50} = 130 µg/ml (24 h)	[200]
Caulerpa scalpelliformis	Methanol extract	Phenolic and flavonoids	Human hepatoma Human cervical adenocarcinoma	Huh-7 HeLa	In vitro	Anti-proliferative and ROS production	*CDC2* gene and *Cas-3* was downregulated and *BAX* was upregulated in both the cell lines. However, the *p53* gene was only upregulated in HeLa cells	ROS inhibition (54%) ROS inhibition (30%)	EC_{50} = 140 µg/ml (24 h) EC_{50} = 200 µg/ml (24 h)	[200]
Ulva lactuca	–	Polysaccharide	Mouse ascetic hepatoma	H22-bearing mice	In vivo	Anti-proliferative	Stimulating the expression of p53 and BAX/Bcl-2 ratio, reducing the expression of P13K/AKT/mTOR pathway, and inhibiting TRAF/TNF-α and CD31/VEGF	Tumor growth inhibition = 74.41%	0.3 ml of 300 mg/kg ULP	[201]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Chaetomorpha sp.	Ethanol extract	Terpenes	Breast cancer	MDA-MB-231	In vitro	Anti-proliferative and radical scavenging	NF-κB signaling and mitochondrial pyruvate dehydrogenase kinase enzyme was inhibited	–-	Anti-proliferative: IC_{50} value = 225.18 µg/ml Antioxidant: IC_{50} value = 9.41 µg/ml	[202]
Udotea flabellum	Sulfated galactans	Sulfated polysaccharide fractions F-I and F-II	Murine melanoma	B16-F10	In vitro	Anti-adhesive, anti-migratory, and anti-proliferative on fibronectin-coated surface	Inhibits adhesion and proliferation by binding to fibronectin in extracellular matrix with fibronectin being its molecular target	Anti-adhesive = ~50% Anti-migratory = ~50% Anti-proliferative = ~40%	Conc. = 1 µg/ml Conc. = 0.1 µg/ml Conc. = 1 µg/ml	[203]
Caulerpa cupressoides var. *flabellata*	––	Sulfated polysaccharide fractions CCB-F0.5 and CCB-F1.0	Murine Melanoma	B16-F10	In vitro	Anti-migratory, anti-proliferative, and melanin production inhibition	Interferes in primordial stage of cancer development. Melanin production is inhibited either by reducing the expression levels of melanogenic factors or through antioxidant activity	Inhibit cell colony formation = 80–90% Anti-migratory effect = 40–75% Inhibits melanin production = ~20%	1000 µg/ml	[204]
Enteromorpha compressa	Aqueous extract	–	Ehlrich ascites carcinoma	EAC	In vitro	Apoptosis	Induction of mitochondria-dependent apoptotic program	–	IC_{50} = 95.35 µg/ml	[205]
Codium decorticatum	Glycoprotein	Polysaccharide	Breast cancer Cervical carcinoma Lung cancer	MCF-7 Siha A549	In vitro	Apoptosis	Cytotoxic to cancer cells by inducing cell membrane damage and releasing LDH enzyme	–	IC_{50} = 45 µg/ml (48 h) IC_{50} = 50 µg/ml (48 h) IC_{50} = 40 µg/ml (48 h)	[206]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Ulva lactuca	–	Polysaccharide	Breast cancer	DMBA administered Wister rats MCF-7	In vivo In vitro	Apoptosis and anti-proliferative Cytotoxicity	Inhibits anti-apoptotic marker and bcl2 expression and elevates the level of pro-apoptotic and p53 protein	Normal duct, lobuloalveolar units, and acini with cuboidal epithelium lining Survival % of MCF-7 = ~ 60%	Single-dose of 25 mg/kg body weight of DMBA and 50 mg/kg body weight of ulvan polysaccharide every other day for 10 weeks IC_{50} = 224.716 µg/ml	[106]
Ulva fasciata Delile	Guai-2-en-10α-ol	Terpene	Triple-negative breast cancer	MDA-MB-231	In vitro	Anti-proliferative	Downregulation of EGFR inhibited the functioning of key proteins of EGFR/P13K/Akt pathway and cell cycle arrest in G1 phase was also observed	Inhibition = 55–60%	IC_{50} = 17.35 µM (24 h)	[207]
Ulva lactuca	Water extract	Polysaccharide	Hepatocellular carcinoma Human breast cancer Cervical cancer	HepG2 MCF-7 HeLa	In vitro	Cytotoxicity	May be due to low cell reactivity to Ulex europaeus-1 lectins	Cell viability = 0% for all the three cell lines at 100 µg/ml	IC_{50} = 29.67 µg/ml IC_{50} = 25.09 µg/ml IC_{50} = 36.33 µg/ml	[147]
Gayralia oxysperma	Sulfated heterorhamnans	Sulfated polysaccharide fractions: OX OXS OXSb OXSc	Human glioblastoma	U87MG	In vitro	Cytotoxicity and cell cycle arrest	Increase in cell number in G_1 phase and mRNA expression levels of p53 and p21	Reduction in cell viability = 48.4% Reduction in cell viability = 46.1% Reduction in cell viability = 26.6% Reduction in cell viability = 28%	100 µg/ml for 48 h	[208]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Ulva intestinalis	–	Sulfated polysaccharide	Human hepatoma	HepG2	In vitro	Apoptosis	Induce the mitochondrial/caspase apoptotic pathway by enhancing the expression of Bax, cleaved caspase-3/-9, PARP, decreasing the expression of Bcl-2, loss of mitochondrial membrane potential, and cytochrome c release	Apoptotic cells = 30.2% (100 µg/ml) Apoptotic cells = ~40% (200 µg/ml) Apoptotic cells = 62% (400 µg/ml)	IC_{50} = 98.5 µg/ml	[149]
Codium decorticatum	Glycoprotein	Polysaccharide	Breast cancer	MDA-MB-231	In vitro	Apoptosis	Induction of ROS dependent mitochondrial intrinsic apoptotic pathway by enhancing the Bax/Bcl-2 ratio, caspase-3/-9 cascade, loss of mitochondrial membrane potential, and cytochrome c release. In addition, the cell cycle gets arrested at the G_2/M phase, and the production of ROS increases	Apoptotic cells = ~60% ROS generation = 62%	IC_{50} = 55 µg/ml (24 h)	[209]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Ulva fasciata	Methanolic extract	–	Human cervical adenocarcinoma Human breast carcinoma (estrogen positive) Human breast carcinoma (estrogen negative) Human hepatocellular carcinoma Human colon carcinoma	HeLa MCF-7 MDA-MB-231 HepG2 HT-29	In vitro	Cytotoxicity and apoptosis	Number of cells increased in Sub-G_1 phase	–	At 72 h: IC_{50} = 54 µg/ml (72 h) IC_{50} = 33 µg/ml (72 h) IC_{50} = 84 µg/ml (72 h) IC_{50} = 100 µg/ml (72 h) IC_{50} = 400 µg/ml	[210]
Capsosiphon fulvescens	Glycoprotein	Polysaccharide	Human gastric carcinoma	AGS	In vitro	Anti-proliferative, anti-migratory, and apoptosis	Inhibits TGF-β1-activated FAK/P13K/AKT pathways, thereby downregulating integrin expression	Anti-proliferative = 50% Apoptotic = 42.68%	At 24 h: Anti-proliferative = 20 µg/ml Apoptotic = 20 µg/ml Anti-migratory = 20 µg/ml	[211]
Capsosiphon fulvescens	Glycoprotein	Polysaccharide	Human gastric carcinoma	AGS	In vitro	Anti-adhesive, anti-migratory, and apoptosis	Inhibits Wnt-1 signaling, β-catenin, and transcription factors. Additionally, cell cycle arrest was observed in G_0/G_1 phase	Cell cycle arrest = 73.1%	Cell cycle arrest = 20 µg/ml (24 h)	[212]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Red seaweeds										
–	3,6-anhydro-L-galactose	Agar-derived sugar	Human colon cancer	HCT-116	In vitro	Anti-proliferative, and apoptosis	Induction of cell viability and apoptosis. Apoptosis was induced by reducing the level of Bcl-2 and enhancing Bax expression, caspase-3, caspase-9, p53, and PARP	Cell viability ~ 10%	100 µg/ml (72 h)	[213]
Gelidium latifolium	Ethanolic extract	–	Murine melanoma	B16-F10	In vitro	Anti-proliferative, cytotoxicity and induction of apoptosis	Mitochondria-mediated intrinsic pathway was promoted for apoptosis with increasing *p53*, *Bax*, *Bak* expression and decreasing *Bcl2* expression	Apoptotic cells = 66.83%	IC_{50} = 84.29 µg/ml	[214]
Pyropia yezoensis	Galactan fractions: GPY_{crude} GPY_{300} GPY_{10} GPY_{10}	Sulfated polysaccharide	Human prostate cancer	DU145 PC-3	In vitro	Anti-proliferative	Increases ROS generation, expression of Bax, initiator caspase-8 and -9, and executor caspase-3; targets P13K/AKT/mTOR pathway	Loss cell viability = 64% Loss cell viability = 68% Growth inhibition = 80% (750 µg/ml) Growth inhibition = 73% (750 µg/ml)	IC_{50} = 100 µg/ml	[215]
Pyropia yezoensis Sookwawon 124	Gamma irradiated PYSP at doses 20 and 100 kGy: PYSP-20 PYSP-100	Polysaccharide	Breast cancer Human cervical adenocarcinoma Liver cancer	MDA-MB-231 HeLa Hep3B	In vitro	Anti-proliferative	mRNA expression levels of cyclin B1 and *Cdk1* was downregulated while that of *P53* and *P21* was upregulated	Inhibition %: PYSP-20 ~ 45% PYSP-100 ~ 37% PYSP ~ 50% PYSP-20 ~ 50% PYSP-100 ~ 49% PYSP ~ 53% PYSP-20 ~ 47% PYSP-100 ~ 53%	Conc. = 200 µg/ml (48 h)	[216]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Pyropia yezoensis Chonsoo2	Native and Gamma irradiated PYP at doses 20 and 50: PYP PYP-20 PYP-50	Porphyran	Human cervical adenocarcinoma Breast cancer Liver cancer	HeLa MDA-MB-231 Hep3B	In vitro	Anti-proliferative and arrests G2/M phase	Cyclin B1 and *Cdk1* had lower levels of mRNA expression while *P53* and *P21* had higher amounts	Inhibition %: PYP = 75% PYP-20 = ~50% PYP-50 = ~50% PYP-20 = ~41% PYP-50 = ~43% PYP = ~80% PYP-20 = 40% PYP-50 = 25%	Conc. = 200 µg/ml (48 h)	[217]
Chondrus armatus	Native carrageenan: κ-carrageenan λ-carrageenan Degraded carrageenan: κ-carrageenan λ-carrageenan	Polysaccharide	Human esophageal adenocarcinoma Squamous cell carcinoma	FLO1 KYSE30	In vitro	Antimetabolic	Induces anti-inflammatory cytokine (IL-10) and mediates TLR pathway (λ-carrageenan) or TLR-independent pathway (κ-carrageenan)	FLO1: Reduction in metabolic activity = 83.3–100.8% Reduction in metabolic activity = 79.1–80% KYSE30: Reduction in metabolic activity = 47–52.5% Reduction in metabolic activity = 55.1–56.2% FLO1: Reduction in metabolic activity = 31.2–57.8% Reduction in metabolic activity = 55.7–74.1% KYSE30: Reduction in metabolic activity = 62.3–64.6% Reduction in metabolic activity = 64.3–76.8%	Conc = 400 µg/ml (24 h)	[218]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Laurencia obtusa	–	Sulfated polysaccharide	Acute monocytic leukemia	THP-1	In vitro	Apoptosis	Immunostimulation of certain immune cells (NK cells, T and B cells, macrophages) and pro-inflammatory cytokines	Apoptosis = 98.1% (200 µg/ml)	EC_{50} = 53 µg/ml	[150]
Hypnea musciformis	κ-carrabiose	Polysaccharide	Murine mammary adenocarcinoma Human ovarian cancer Myelogenous leukemia Mouse melanoma Mouse bladder cancer Human lung cancer Murine cutaneous squamous cell carcinoma	LM2 IGROV-1 K562 B16-F10 MB49 A549 Pam212	In vitro	Cytotoxicity and anti-migratory	Induction of the arrest of G2/M phase and apoptosis	Migration index = 0.52 (0.05 mg/ml) At 0.06 mg/ml, sub-G1 populations increased to 21.3% and an arrest in S phase increased to 13.6% in LM2 cells	At 48 h: IC_{50} = 0.043 mg/ml IC_{50} = 0.099 mg/ml IC_{50} = 0.049 mg/ml IC_{50} = 0.039 mg/ml IC_{50} = 0.045 mg/ml IC_{50} = 0.066 mg/ml IC_{50} = 0.051 mg/ml	[219]
Palisada perforate (formerly known as *Laurencia papillosa*)	κ-carrageenan (LP-W1) ι-carrageenan (LP-W2) λ-carrageenan (LP-W3)	Sulfated polysaccharide	Human breast cancer	MCF-7	In vitro	Apoptosis	Reduction in cell viability by increasing apoptotic activity and induction of ACTIVE-CASPASE-3, PARP, *Bax* gene and *p53* gene	At 72 h: Cell viability = 51.8% Cell viability = 18.4% Early apoptosis = 26% Late apoptosis = 30% Cell viability = 22.7% Early apoptotis = 7% Late apoptosis = 54%	IC_{50} = 200 µM IC_{50} = 50 µM IC_{50} = 25 µM	[220]
Iridaea cordata *Pyropia endiviifolia*	Ethyl acetate Hexane extract	–	Human epidermoid carcinoma	A-431	In vitro	Cytotoxicity	–	Inhibitory ratio = 91.1% Inhibitory rate = 56.6%	Conc = 500 µg/ml (24 h)	[221]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Acanthophora spicifera	–	Sulfated polysachharide	Human lung cancer	A549	In vitro	Cytotoxicity and apoptosis	Cytotoxic to A549 cells by swelling, crooking of membrane and chromatin condensation	–	IC_{50} = 400 µg/ml (48 h)	[222]
Asparagopsis armata *Sphaerococcus coronopifolius* *Asparagopsis armata* *Sphaerococcus coronopifolius*	Dichloromethane extract Methanol extract	Polysaccharide	Human colorectal cancer	Caco-2	In vitro	Antiproliferative and cytotoxicity	–	Loss of cell viability = 98.96% Anti-proliferative = 100% Loss of cell viability = 98.08% Anti-proliferative = 99.04% Loss of cell viability = 92.68% Loss of cell viability = 96.47%	Conc. = 1 mg/ml (24 h) for all Cytotoxicity: IC_{50} = 21.3 µg/ml Anti-proliferation: IC_{50} = 36.5 µg/ml	[223]
Gracilaria fisheri	Sulfated galactans	Polysaccharide	Cholangiocarcinoma	HuCCA-1 RMCCA-1	In vitro	Anti-migration	Decrease MMP-9, expression of p-FAK, blocks phosphorylation of EGFR, ERK, increases expression of E-cadherin, and inhibits MAPK/ERK signal transduction pathway	Distance of wound closure = 40.6% Distance of wound closure = 21.1% (24 h) (100 µg/ml)	IC_{50} = 7 µg/ml Conc = 100 µg/ml (24 h) IC_{50} = 8 µg/ml Conc = 100 µg/ml (24 h)	[224]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Pterocladiella capillacea	Mertensene	Hlaogenated monoterpene	Human colon adenocarcinoma	HT-29 LS174	In vitro	Apoptosis, and cell cycle arrest	Inhibition of cell viability and induction of caspase-dependent apoptotic pathway via activation of MAPK ERK-1/-2, AKT, and NF-κB pathways. Moreover, mertensene is 2.4 to 3.7 fold toxic against LS174 and arrest G2/M phase in HT-29	Apoptotic cells = 20% Apoptotic cells = 38% Apoptotic cells = 46.7%	Conc. = 50 µg/ml (72 h) Conc. = 70 µg/ml (72 h) Conc. = 90 µg/ml (72 h) Cell viability: IC_{50} = 56.50 µg/ml IC_{50} = 49.77 µg/ml	[225]
–	λ-carrageenan	Sulfated polysaccharide	Human mammary carcinoma	MCF-7	In vitro	Anti-angiogenesis	Inhibition of the degradation of heparin sulfate present in extracellular matrix by heparanase to prevent pseudo-vessel formation	Slowing pseudo-vessel formation = 32% (FBS-free medium) Slowing pseudo-vessel formation = 48% (heparanase-rich medium)	Conc. = 200 µg/ml	[226]
Gracilariopsis lemaneiformis	–	Polysaccharide	Human lung cancer Human gastric cancer Mouse melanoma	A549 MKN28 B16	In vitro	Anti-proliferative and apoptosis	Upregulation of Fas/FasL-mediated apoptotic pathway	At 72 h: Cell proliferation inhibition = 41.376% Cell proliferation inhibition = 47.134% Cell proliferation inhibition = 52.151%	Anti-proliferative: IC_{50} = 50 µg/ml (48 h) IC_{50} = 78 µg/ml (48 h) IC_{50} = 90 µg/ml (48 h) Apoptotic: Conc = 60 µg/ml	[227]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Kappaphycus alvarezii	Native carrageenan	Sulfated polysaccharide	Breast carcinoma Colon carcinoma Liver carcinoma Osteosarcoma	MCF-7 HT-29 Hep-G2 MG63	In vitro	Cell viability and growth inhibition	Induction of apoptosis via both mitochondrial- and death receptor-mediated pathways	Reduction in cell viability = 43.63% (150 µg/ml) Growth inhibition = 56.37% (150 µg/ml) Growth inhibition = 67.67% (150 µg/ml) Growth inhibition = 64.81% (150 µg/ml) Growth inhibition = 65.70% (150 µg/ml)	IC_{50} = 103.2 µg/ml IC_{50} = 73.87 µg/ml IC_{50} = 56.71 µg/ml IC_{50} = 47.85 µg/ml	[228]
Palisada perforata (formerly known as *Laurencia papillosa*)	–	Sulfated polysaccharide	Breast cancer	MDA-MB-231	In vitro	Apoptosis and cell cycle arrest	Induction of cell death, G_1-phase cell cycle arrest, *Bax* gene and ROS production, and downregulation of *Bcl-2* gene to induce apoptosis	At 24 h: Cell death induction = 52% G_1 phase = 73% Apoptotic cells = 50%	Conc. = 50 µg/ml Conc. = 10 µg/ml Conc. = 50 µg/ml	[229]
Asparagopsis armata *Sphaerococcus coronopifolius* *Asparagopsis armata* *Sphaerococcus coronopifolius*	Dichloromethane extract Methanolic extract	Polysaccharide	Human hepatocellular carcinoma	HepG2	In vitro	Antiproliferative and cytotoxicity	–	Cell viability = 11.22% Anti-proliferation = 98.56% Cell viability = 12.84% Anti-proliferation = 99.61% Cell viability = 1.51% Cell viability = 14.04%	Conc. = 1000 µg/ml (24 h) Cytotoxicity: IC_{50} = 14.1 µg/ml Anti-proliferation: IC_{50} = 32.3 µg/ml	[230]
Laurencia obtusa	Methanolic extract	–	Breast cancer	MCF-7	In vitro	Apoptosis	–	Inhibition of cell viability = 82.86%	IC_{50} = 99.1 µg/ml	[231]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Brown seaweed										
Sargassum pallidum	–	Sulfated polysaccharide fractions: SPP-1 and SPP-0.7	Human lung cancer Human hepatoma Murine melanoma	A549 HepG2 B16	In vitro	Anti-proliferative and apoptosis	Increase in the activity of lymphocytes, macrophages, and serum cytokines such as IL-6, IL-1β, iNOS, TNF-α. Expression of genes related to TGF-β signaling, RIG-I-like receptor signaling, p53 signaling, and hippo signaling mediates anti-tumor activity	Inhibitory rate = 64.28% (SPP-0.7) Apoptotic rate = 7.99% Apoptotic rate = 8.01% Apoptotic rate = 3.62% Inhibitory rate = 39.26% (SPP-1) Inhibitory rate = 30.06% (SPP-0.7)	Conc. = 100 µg/ml Conc. = 25 µg/ml Conc. = 100 µg/ml Conc. = 400 µg/ml Conc. = 400 µg/ml Conc. = 25 µg/ml	[232]
Sargassum polycystum	Fucoidan (low molecular weight fraction)	Sulfated polysaccharide	Human leukemia Human breast cancer	HL-60 MCF-7	In vitro	Apoptosis	Mitochondria-mediated apoptotic pathway, G_1 phase cell cycle arrest	–	IC_{50} = 84.63 µg/ml IC_{50} = 93.62 µg/ml	[233]
Hizikia fusiforme	Fucose	Sulfated polysaccharide	Human bladder cancer EJ tumor xenografts	MGH-U1 Balb/C nude mice	In vitro In vivo	Anti-proliferative	G_1 phase cell cycle arrest and inhibits MMP-9 expression Decline in the number of cancer cells	–	IC_{50} = 800 µg/ml Conc. = 20 mg/kg (5 days)	[234]
Sargassum linearifolium *Cystoseira crinita*	Hot aqueous extract Cold methanolic extract	–	Human breast adenocarcinoma	MCF-7	In vitro	Apoptosis and autophagy	Increased mRNA expression levels of Bax, and Beclin-1 and decreased expression of Bcl-2	–	IC_{50} = 31.1 µg/ml IC_{50} = 18.0 µg/ml	[235]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Sargassum hemiphyllum	Oligo-fucoxanthin	–	Human liver cancer	HepG2	In vitro	Apoptosis and cell cycle arrest	Suppression of cell viability, cell cycle arrest in G_1 phase and induction of apoptosis via activation of caspase-8/-9 and regulating the expression of lncRNA profile	Loss of cell viability = 81.34% G_1 phase = 39.5%	Conc. = 50 µg/ml Conc. = 50 µg/ml	[236]
Fucus vesiculosus	Hydrothermal treated fucoidan	Polysaccharide	Burkitt lymphoma	Raji	In vitro	Anti-proliferative	–	Reduced viable cells = 88%	Conc. = 150 µg/ml (72 h)	[237]
Sargassum fusiforme	–	Polysaccharide	Nasopharyngeal carcinoma cell line; CNE cells were injected into axilla of left hind leg	Balb/c nude mice	In vivo	Anti-proliferative	The growth of tumor was inhibited and the tumor weight was reduced through by increasing the serum levels of IL-1β, TNF-α, nitric oxide, and IgM	Tumor weight = 1.61 g Tumor inhibition rate = 17.9% Tumor weight = 1.42 g Tumor inhibition rate = 27.6% Tumor weight = 1.12 g Tumor inhibition rate = 42.9%	Conc. = 50 mg/kg Conc. = 100 mg/kg Conc. = 200 mg/kg	[238]
Sargassum fusiforme	–	Polysaccharide	Human hepatoma HepG2 cells inoculated in mice	HepG2 Balb/c nude mice	In vitro In vivo	Anti-proliferative and apoptosis	Increase in the level of Bax protein and decrease in Bcl-2 protein Tumor growth was inhibited and the weight of the tumor was reduced	Apoptotic cells = 8.1% Apoptotic cells = 16.1% Apoptotic cells = 50.7% Apoptotic cells = 40.1% Apoptotic cells = 43.2% Tumor weight = 1.46 g Tumor weight = 1.25 g Tumor weight = 0.99 g	IC_{50} = 1158.6 µg/ml Conc. = 125 mg/ml Conc. = 250 mg/ml Conc. = 500 mg/ml Conc. = 1000 mg/ml Conc. = 2000 mg/ml Conc. = 100 mg/kg Conc. = 200 mg/kg Conc. = 400 mg/kg	[239]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Dictyota dichotoma *Dictyota spiralis*	Cold methanolic extract	–	Breast cancer	MCF-7	In vitro	Apoptosis	–	Inhibition of cell viability = 91.32% (50 µg/ml) Inhibition of cell viability = 82.14%	IC_{50} = 17.2 ng/ml IC_{50} = 35.9 µg/ml	[231]
Turbinaria conoides	Fucoidan	Sulfated polysaccharide	Human lung adenocarcinoma	A549	In vitro	Anti-proliferative, apoptosis, and cell cycle arrest	Growth-inhibitory activity, and cell cycle arrest in G_0/G_1 phase	Cell number in G_0/G_1 phase = 76.3% (24 h) Cell number in G_0/G_1 phase = 78.86% (48 h) Cell proliferation decreased by 3.5 fold	GI_{50} = 75 µg/ml Conc. = 5 µM	[240]
–	Fucoxanthin	Sulfated polysaccharide	Human glioma	U87 U251 BALB/c-nude mice injected with U87 cells	In vitro In vivo	Anti-proliferative and apoptosis	Activates apoptosis by inhibiting P13K/Akt/mTOR pathway and suppresses invasion and migration by blocking p38-MMP-2/9 pathway Reduced tumor volume and weight	Apoptotic rate = 14.32 Apoptotic rate = 28.36 Apoptotic rate = 17.00 Apoptoric rate = 27.31 Reduced tumor volume = 1644 mm^3	Conc. = 25 µM Conc. = 50 µM Conc. = 25 µM Conc. = 50 µM Conc. = 200 mg/kg/day	[241]
Fucus vesiculosus	Fucoidan	Sulfated polysaccharide	Diffuse large B cell lymphoma	SUDHL-4 OCI-LY8 NU-DUL-1 TMD8 U2932 DB OCI-LY8 Injected NOD/SCID mice	In vitro In vivo	Anti-proliferative, apoptosis and cell cycle arrest in G_0/G_1	Induction of G_0/G_1 cell cycle arrest, caspase-dependent cell apoptosis, p21 upregulation and cyclin D1, Cdk4, Cdk6 downregulation Fucoidan reduced tumor volume and tumor weight in xenograft mouse model	G_0/G_1 cell population = 61.21 (24 h) Tumor weight = 0.5 g	Anti-proliferation: IC_{50} = 80 µg/ml IC_{50} = 82.3 µg/ml IC_{50} = 93.7 µg/ml IC_{50} = 97.5 µg/ml IC_{50} = 101.6 µg/ml IC_{50} = 95.5 µg/ml Conc. = 100 mg/kg/day for 21 days	[242]

Table 2 (continued)

Seaweed	Compound/extract	Class of compound	Type of cancer	Model/cell line	In vitro/in vivo	Activity	Signaling	Effect	Dose	References
Dictyota cilliolata Dictyota menstrualis	Methanolic extract	–	Human cervical adenocarcinoma	HeLa	In vitro	Cytotoxicity and apoptosis	Induction of mitochondria-dependent apoptotic pathway by activation of caspase-3 and −9, and cell cycle arrest in S phase in MEDC	Cell viability inhibition rate = 50% Apoptotic cells = 4.32% Cell viability inhibition rate = 80% Apoptotic cells = 14.9%	Conc. = 0.2 mg/ml (72 h) Conc. = 0.2 mg/ml (48 h)	[243]
Ascophyllum nodosum	Ascophyllan	Sulfated polysaccharide	Murine melanoma B16 melanoma cells injected into tail vein	B16 C57BL/6 mice	In vitro In vivo	Anti-adhesive anti-migratory Anti-metastatic	Inhibition of cell adhesion and invasion by reducing the level of N-cadherin, MMP-9 and enhancing the level of E-cadherin Decline in the number of metastatic nodules on the lung surface	Cell adhesion inhibitory activity = 47% Cell adhesion inhibitory activity = 62% Cell adhesion inhibitory activity = 69% Invasion inhibition = 57% Invasion inhibition = 67% Invasion inhibition = 78% Anti-proliferative	Cell adhesion inhibition: Conc. = 10 µg/ml Conc. = 100 µg/ml Conc. = 1000 µg/ml Invasion inhibition: Conc. = 5 µg/ml Conc. = 10 µg/ml Conc. = 20 µg/ml Conc. = 25 mg/kg/day	[244]

inhibition via the CagA protein, which is involved in the c-Met-PI3K/Akt-mTOR signaling pathway, was identified as a confirmation of GC development [257]. Bromophenol and its derivatives (BOS-93 and BOS-102) from marine algae have been shown to inhibit and downregulate the PI3K/Akt/mTOR and MAPK signaling pathways, as well as Bcl-2, MMP, and Cyt-c expression, while upregulating ERK, Bax, Atg14, beclin-1, and phosphorylated p38 expression thereby stimulating apoptosis and preventing carcinogenesis [258]. Inflammation has long been a key factor in the development of cancer. CagA protein and peptidoglycan, as well as activating TLRs, NF-κB, TNF-α, STAT-3, IL-1β, IL-2, IL-4, IL-8, IL-10, IL-12, TNF, IFN, epidermal growth factor response (EFGR), and COX-2/prostaglandin E2 (PGE2) pathways, cause gastric inflammation [44, 159, 249, 259]. Apart from TLR/MYD88 adapter signaling, COX-2 stimulation, as well as Wnt signaling activation and β-catenin accumulation, promotes carcinogenesis. Furthermore, activating PI3K and MAPK signaling via PGE2 signaling causes the growth of CD33 + CD44 + cancer stem cells [159]. Astaxanthin and fucoxanthin from various microalgae and macroalgae have been found to inhibit tumor/cancer progression in vitro experiments by regulating and preventing cell cycle arrest, p27 expression, ERKs expression, NF-κB expression, MMP-2/9 expression, and apoptosis induction [247]. Moreover, the ability of human carcinoma MKN45 gastric cells to invade was shown to be inhibited by a new polysaccharide derived from brown algae (*Sargassum* sp.). In cancer cells, this polysaccharide caused JNK phosphorylation, p53, Caspase-3 and 9, and ROS, halting the cell cycle (G2/M phase) and triggering apoptosis through the ROS/JNK signaling pathway [260]. This polysaccharide, on the other hand, had no effect on migration and no effect on p38 MAPK signaling or downstream MMP-9/2 [261]. Moreover, porphyran from *Porphyra* sp. has anticancer characteristics that inhibit in vitro adenocarcinoma cell lines (AGS) by triggering apoptosis via the mitochondrial pathway [262]. Apart from dislodging *H. pylori* from human AGS cells, fucoidan fraction (Fucus B) has been shown to cause dose-dependent cytotoxicity in AGS cancer cells, which was verified using a lactate dehydrogenase assay. Additionally, 6 gms of fucoidan taken regularly seems to be non-toxic and has the potential for use in treating *H. pylori* infection and GC formation [263]. Inflammation-mediated GC is accelerated by other inflammatory cytokines (CXCL1, CXCL2, CXCL5, CCL3, CCL4, and TLR2) under COX2/PGE2 signaling [264]. At 100 mg/kg/day, a carotenoid-rich acetone extract of *Chlorococcum* sp. decreased inflammation, lowered IFN-γ and IL-4 levels in splenocytes, and lowered bacterial density in infected BALB/c mice [265]. Furthermore, brown algae sulfated polysaccharides (fucoidan) have been shown to decrease the expression of IL-1β, IL-6, iNOS, PGE2, NO, and TNF-α. In addition, the anti-inflammatory fucoidan has suppressed complement-related inflammation in the stomach wall [254]. As indicated before, it has been demonstrated that phycobiliproteins from cyanobacteria reduce the production of pro-inflammatory cytokines including NO and COX-2 [266]. Furthermore, oxidative stress caused by H. pylori in the gastric cells contributes to GC. In addition to CagA's fatal impact, pro-oxidant activities like host spermine oxidase, NADPH oxidase, or mitochondria-mediated ROS production reduce antioxidant or glutathione activity in *H. pylori*-infected patients. Furthermore, nitric oxide (NO) produced in macrophages, gastric cells, and lymphocytes causes DNA adducts and nitrotyrosine, instigating DNA and protein damage [249]. It has been demonstrated that the antioxidant properties of polysaccharides, carotenoids, lipids, peptides, and pigments of micro- and macroalgae can repair ROS-induced damage in cancer cells, as previously mentioned in this review. Consumption of antioxidant or selenium supplements at the same time not only replenishes SOD, catalase, and glutathione levels but also regulates positive gene expression on intracellular and intercellular signaling, preventing deadly damage in GC [267]. Nonetheless, using algae in combination with conventional antibiotics to treat antimicrobial-resistant *H. pylori* infection and prevent GC may be beneficial. Because these bacteria have developed resistance and there is no cure or prophylactic available, more progress in developing vaccines using biomedical approaches is required.

Biomedical approaches

The development of biomaterials has become one of the foremost significant fields of research in contemporary science, with tremendous promise for biological applications [268]. Furthermore, due to their non-toxic, biodegradable, and biocompatible properties, the biological exploration of natural materials has risen [152]. Despite the fact that various biomaterials have been employed as biological agents to combat drug resistance. Algae, a ubiquitous photosynthetic organism, has long been regarded as interesting naturally active biomaterials with a range of applications including drug administration, bioengineering, wound repair, bioanalysis, and hypoxia-mediated tumor therapy [268]. Microalgae have demonstrated strong targeted drug delivery capabilities in both in vitro and in vivo investigations, with an emphasis on anticancer effects, by loading drug molecules through their active surfaces. Microalgae (*Spirulina platensis*)-based oral medication delivery systems containing (SP@Curcumin) have been shown to be easily trapped and

adhered to intestinal villi and wall, in contrast to conventional oral drug delivery problems. In colon cancer and colitis, the SP@Curcumin has been studied for its ability to operate as a radioprotector by scavenging ROS generated by healthy tissues after X-ray exposure, as well as lowering pro-inflammatory cytokine production and increasing drug bioavailability [269]. Additionally, it has been demonstrated that *C. reinhardtii* that has been engineered to contain chitosan-coated iron oxide nanoparticles (CSIONPs) coupled to the chemotherapeutic medication doxorubicin (DOX) enhances the drug uptake in SK-BR3 cancer cells [270]. Simultaneously, the development of *Spirulina* sp. as a biotemplate-based magnetic microrobot ((Pd@Au)/Fe3O4@Sp.-DOX) exhibited excellent synergistic chemo-photothermal therapeutics for both 769P and EC109 cancer cells [271]. When combined with cell-targeting antibodies and chemotherapeutic chemical molecules (camptothecin and 7-ethyl-10-hydroxy-camptothecin), genetically modified biosilica frustules from the altered diatom *Thalassiosira pseudonana* specifically targeted and killed in vivo neuroblastoma cells in mice models (SH-SY5Y) [272]. Furthermore, it has been demonstrated that lung-targeted administration of positively charged DOX molecules using negatively charged *S. platensis* kills 4T1 and CT26 tumor cells [273]. Furthermore, tumor hypoxia is caused by unregulated cell proliferation, altered metabolism, and aberrant tumor blood cells, all of which result in inadequate oxygen and nutrient transfer. Hypoxia causes cell cycle arrest, suppresses apoptosis and cell death, modifies the activity of the p53 gene and the mitochondria, expresses the drug efflux pump (P-gp), and reduces oxygenation in the case of chemotherapy cytotoxicity [274]. Since the ROS generated by photodynamic treatment (PDT) and radiation therapy (RT) are converted from oxygen, these two therapeutic modalities rely largely on oxygen. Living algae are therefore anticipated to boost cellular oxygen levels through photosynthesis, acting as a source for the production of ROS and thereby boosting the impact of PDT/RT [268]. *Spirulina* sp. and *Chlorella* sp. are microalgae that help to reduce tumor hypoxia by acting as oxygenators in in vivo tumor synergistic therapies (PDT, RT, or PDT/RT) [269]. A cancer-targeted theranostic approach involving biohybrid microswimmers based on engineered *S. platensis* has been shown to increase oxygen generation in a 4T1 bearing mouse model, as well as innate chlorophyll and magnetic resonance derived fluorescence and photoacoustic imaging for monitoring effective tumor therapy procedures and modifying tumor microenvironment hypoxia [275]. Additionally, an autotrophic light-triggered green affording oxygen engine (ALGAE) made of calcium alginate and *C. pyrenoidosa* was implanted into 4T1 tumor-bearing mouse tumors. This engine was triggered three times to induce hypoxia-resistant PDT and successfully limit tumor growth and metastasis [269]. Mice with 4T1 tumors were given an intravenous injection of a modified *C. vulgaris*-based biohybrid Algae@SiO2 system, which inhibited tumor growth. Moreover, ROS generated from Algae@SiO2-derived chlorophyll induces cytotoxicity to cancer cells throughout the photodynamic therapy [276]. In addition, in breast tumors (4T1) and ovarian tumors (SKOV3) mice models, the red blood cell membrane (RBCM) was included in the surface modification of *C. vulgaris* dramatically lowering tumor development, hypoxia-dependent radioresistance, angiogenesis, and proliferation, triggering death. Downregulation of HIF1 and VEGF, as well as a decrease in Ki67 and CD31 expression, raises cleaved caspase-3, which aids in apoptosis induction and could lead to the development of algae-mediated hypoxia-related tumor therapy in the future [277].

Macroalgae-derived bioactive compounds have a vast array of biomedical applications. Among them, the priority focus is on polysaccharides due to their maximum content in green, brown, and red algae [10]. They are considered advantageous therapeutically as they are biocompatible, non-toxic, biologically tunable, and biodegradable [152]. The presence of biologically active metabolites in seaweeds has gained attention as food supplements in East Asia for centuries. Polysaccharides from macroalgae act as dietary fibers stimulating the production and thickness of intestinal mucus, thus protecting against carcinogenic compounds. Consumption of recommended intake of seaweeds can prevent colon, rectal, stomach, and breast cancer [2, 278–280]. Dietary intake of *Laminaria* sp., *Saccharina* sp., *Undaria pinnatifida*, and *Porphyra/Pyropia* sp. are all known to reduce the risk of breast cancer [278, 281]. Through the activation of NK cells, macrophages, and T cells, seaweeds have immunomodulating properties that enable them to recognize cancer antigens and harm target cells while also enhancing the immune system to prevent the growth of cancer [2]. *Laminaria digitata*-derived Laminarin stimulated the maturation of dendritic cells and production of T_c cells, IFN-γ, and TNF-α at a concentration of 25 mg/kg to inhibit B16-ovalbumin melanoma tumor growth and metastasis in a mouse model [282]. According to research by Sun et al. [283], fucoidan from Fucus vesiculosus suppressed MHCC-97H (human hepatoma cell line) motility by downregulating CCL22 in M2 macrophages, hence reducing NF-B-dependent transcription. Specifically, the seaweed polysaccharides being hydrophilic are suitable to act as drug delivery agents for hydrophobic anticancer

drugs. Nevertheless, these polysaccharides have the ability to reduce the side effects of drugs, prevent the dispersion of chemotherapeutic agents throughout the body as well as optimize the release of anticancer compounds [284]. Oligocarrageenan obtained from the *K. alvarezii* κ-carrageenan was modified with polycaprolactone (PCL) chains to form PCL-grafted oligocarrageenan nano-micelles (187 nm) that encapsulated curcumin (hydrophobic drug). This enhanced the anti-inflammatory activity in TNF-triggered inflammatory trials [285]. Hydrophobic anticancer compound docetaxel is encapsulated with fucoidan-poly(lactic-co-glycolic acid) nanocarrier (FPN-DTX) [284]. According to Kahya et al. [286], the controlled release of methotrexate is achieved by crosslinking sodium alginate (NaAlg)/sodium carboxymethyl cellulose (NaCMC) composite hydrogel beads with a barium chloride solution. A superabsorbent hydrogel was prepared using carboxymethylagarose (CMA) and polyacrylamide (PAm) while extracting agarose from *Gracilaria dura* and forming CMA-Ag-PAm. The hydrogel showed extensive pH-responsive behavior causing an enhanced release of DOX with a decline in pH from 7.4 to 5.0. This DOX-loaded hydrogel attributes to cytotoxicity against A549 and Hep-G2 cell lines [287]. Nanoparticles derived from macroalgae show a wide spectrum of anticancer properties. In order to create biocompatible silver nanoparticles with an IC_{50} value of 95.35 g/ml against Ehlrich Ascites Carcinoma cell lines, the aqueous extract of *Enteromorpha compressa* is used [205]. Fabrication of methyl gallate encapsulated zeolitic imidazole framework (MG@ZIF-L) prepared from the extracts of *Gracilaria debilis* showed good biocompatibility, high loading capacity, and rapid release of drugs in the tumor microenvironment. The nanocomposite is cytotoxic to A549 (lung cancer cell line) because of enhanced ROS generation, which causes mitochondrial damage and encourages apoptosis. The cytotoxicity of MG@ZIF-L was tested in an in vivo zebrafish embryo model system and found to be non-toxic [288]. The harmful effects of radiotherapy/chemotherapy can be overcome by using protective agents that are derived from macroalgae. In this area, the most exploited compound of seaweeds is phlorotannins. Phlorotannins extracted from *Ecklonia cava* include phloroglucinol, dieckol, eckol, and triphlorethol A that show radioprotection activity against radiation-induced damage and oxidative stress through inhibition of apoptosis [289–291]. Similarly, methanolic extracts of *Polyopes lancifolia* have been found to contain higher amounts of SOD and catalase (cytoprotective enzymes) that demonstrate radioprotective activity via antioxidant processes [292].

Conclusions

The abundance of bioactive components found in algae has aroused the interest of many experts, who have proposed potential applications in the industrial and medical sectors. Over the past few decades, numerous in vitro and in vivo investigations have demonstrated that algae offer a wide range of applications in cancer therapy. By activating either the caspase-dependent or caspase-independent apoptosis pathway, which is followed by the upregulation of various tumor suppressor factors and the downregulation of particular cancer genes, markers, and signaling pathways, it has been shown that these algal-derived components are effective at inducing cytotoxicity and cellular death. Furthermore, these ingredients' anti-adhesive, immunostimulating, and anti-inflammatory properties boost the effectiveness of the anticancer potential that has been shown to be effective in the treatment of *H. pylori*-infected stomach cancer. Algal metabolites therefore can be used to protect humans from various cancers, in addition to their biomedical applications, which are still being studied. Furthermore, based on their molecular weight and viscosity, algal metabolites have been used in a number of other nutraceuticals, proving their plasticity. In the realm of innovative drug development, which replaces manufactured pharmaceuticals, various preclinical investigations using these bioactive components have also been carried out recently. Microalgae have, however, been used much less frequently as anticancer drugs than macroalgal metabolites. Advanced extraction procedures, as well as ideal growth factors and genetic engineering, must be considered for improved metabolite production. Nonetheless, to solve the conundrum, thorough clinical trials and standard dosage recommendations must be devised, allowing the potentiality of these bioactive components to be assessed.

Abbreviations

CDK	Cyclin-dependent kinase
CDC	Cell division cycle
MAP/RAS/RTK	Mitogen-activated protein/rat sarcoma virus/receptor tyrosine kinase
PI3K	Phosphoinositide 3-kinase
TGFβ	Transforming growth factor-beta
NF-κB	Nuclear factor-kappa B
JNK	Jun N-terminal kinases
Ras-ERK	Ras-extracellular signal-regulated kinase
STAT	Signal transducer and activator of transcription
TAM	Tumor-associated macrophages
TAN	Tumor-associated neutrophils
TNF	Tumor necrosis factor
IL	Interleukins
GMCSF	Granulocyte–macrophage colony-stimulating factor
GCSF	Granulocyte colony-stimulating factor
ROS	Reactive oxygen species
SIRT-1	Sirtuin-1
COX	Cyclooxygenase
HES	Hairy and enhancer of split
PC	Prostate cancer

SAPK	Stress-activated protein kinases
mTOR	Mechanistic target of rapamycin
GADD	Growth arrest and DNA damage
FGFR	Fibroblast growth factor receptor
EGR	Early growth response
FGF	Fibroblast growth factor
EPS	Exopolysaccharides
MAA	Mycosporine-like amino acids
ω	Omega
CARD	Caspase recruitment domain
VEGF	Vascular endothelial growth factors
SVCT2	Sodium-dependent vit C transporter2
GLUTs	Glucose transporters
AMM	Antioxidant multivitamin and mineral
ALA	Alpha-lipoic acid
κ	Kappa
μ	Mu
ι	Iota
β	Beta
λ	Lambda
θ	Theta
ν	Nu
BMPs	Bone morphogenetic proteins
ATRA	All-trans retinoic acid
PARP	Poly-ADP-ribose polymerase
micro-LVD	Micro-lymphatic vascular density
VacA	Vacuolating cytotoxin A
CagA	Cytotoxin-associated gene A
cag PAI	Cag pathogenicity island
ER	Endoplasmic reticulum
EFGR	Epidermal growth factor response
CSIONPs	Chitosan-coated iron oxide nanoparticles
ALGAE	Autotrophic light-triggered green affording oxygen engine
RBCM	Red blood cell membrane
MG@ZIF-L	Methyl gallate encapsulated zeolitic imidazole framework

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Declarations

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Not applicable.

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