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REVIEW ARTICLE

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It comes from the sea: macroalgae-derived bioactive compounds with anti-cancer potential

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ABSTRACT

Nature derived compounds represent a valuable source of bioactive molecules with enormous potential. The sea is one of the richest environments, full of skilled organisms, where algae stand out due to their unique characteristics. Marine macroalgae adapt their phenotypic characteristics, such as chemical composition, depending on the environmental conditions where they live. The compounds produced by these organisms show tremendous potential to be used in the biomedical field, due to their antioxidant, anti-inflammatory, immunomodulatory, and anti-cancer properties.

Cancer is one of the deadliest diseases in the world, and the lack of effective treatments highlights the urgent need for the development of new therapeutic strategies. This review provides an overview of the current advances regarding the anti-cancer activity of the three major groups of marine macroalgae, i.e., red algae (*Rhodophyta*), brown algae (*Phaeophyceae*), and green algae (*Chlorophyta*) on pancreatic, lung, breast, cervical, colorectal, liver, and gastric cancers as well as leukemia and melanoma. In addition, future perspectives, and limitations regarding this field of work are also discussed.

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Introduction

The marine environment is an untapped source of unique and efficient compounds with biomedical potential, where algae stand out as an attractive source [1–3]. Marine macroalgae are photosynthetic plant-like eukaryotic organisms classified into three major groups: (1) green algae (*Chlorophyta*); (2) red algae (*Rhodophyta*); and (3) brown algae (*Phaeophyceae*) [4,5]. These organisms grow in very harsh environmental conditions and their chemical composition is greatly influenced by: temperature, pH, sunlight, physiological status, and carbon dioxide supply [4,6]. As a consequence of the seasonal and environmental adaptations, as well as taxonomic diversity, algae produce a wide range of bioactive compounds, such as polysaccharides, enzymes, glycoproteins, polyunsaturated fatty acids, sulfolipids, phenolics, terpenoids, peptides, and other secondary metabolites. These compounds exhibit interesting properties, such as antioxidant, anti-inflammatory, immunomodulatory, and anti-cancer activities, that might have potential therapeutic applications [7–10].

Cancer is a major health concern with multifactorial etiology, including genetic mutations, environmental toxins, immune conditions, unhealthy diets, and hormones [11]. Although cancer is considered an assortment of diseases, all share common cellular and molecular trends [11]. In every country of the world, it is an important barrier to life expectancy, and its burden incidence and mortality are rapidly rising [11]. In fact, in 2020, 19.3 million new cancer cases were diagnosed with 10 million related deaths, being lung (18%), colorectal (9.4%), liver (8.3%), stomach (7.7%), and breast (6.9%) cancer the leading causes [11]. Notwithstanding being less frequent, pancreatic cancer (PC) has the poorest prognosis among all types of cancers, with extremely low survival (only 7% of patients reach 5-year survival) [12].

Despite substantial improvements in modern drug design and manufacturing, cancer treatment still

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depends on surgery resection, chemotherapy, and radiotherapy, with serious side effects and limited curative results [13]. Moreover, immunotherapy, a promising treatment for many cancer types, by stimulating the patient immune system, has shown limited applications in several types of cancer such as pancreatic, or glioblastoma [14,15]. Pancreatic tumors, for example, due to the dense fibrous matrix layer around cancer cells, display an immunosuppressive microenvironment, which explains their resistance to both chemo and immunotherapy treatments [14,16]. Glioblastoma presents a similar multifactorial phenomenon, along with the presence of the blood–brain barrier and the limited knowledge of the neuroimmune system, that plague immunotherapy efficacy [17].

Given the burden of cancer in society, the existing therapeutic options, and side effects, it is urgent to explore different solutions such as the finding of new compounds with anti-cancer activity [9,18,19]. The discovery of compounds with anti-cancer potential is actively growing [9]. This review will innovatively discuss the last five years' current advances in the three major groups of marine macroalgae, i.e., brown, red, and green-derived compounds on several types of cancer, as well as the future perspectives and limitations.

Macroalgae compounds with anti-cancer potential

Macroalgae are multicellular organisms that live in water or humid places [17]. They can perform photosynthesis which transforms light into chemical energy using carbon dioxide to create complex organic compounds with biological activity, and during the process of organic synthesis, oxygen (O_2) is released [17]. As a result of their photosynthetic activity, macroalgae are the main producers of the Earth's O_2. Although the interest of the scientific community in these organisms is increasing, they are still an underused natural resource with great potential, namely for biomedical applications [16–18].

Recently, many reviews were published compiling the scientific literature about the anti-cancer potential of marine macroalgae [1,9,19,20]. This review compiles the last five years' research on several species of brown, green, and red macroalgae derived compounds with anti-cancer effects over pancreatic, lung, breast, cervical, colorectal, liver, gastric, leukemic, and melanoma cancer models. Additionally, the mechanisms underlying these anti-cancer actions of algae specific compounds will be discussed. Different types of extractions led to obtaining different types of compounds, such as polysaccharides, enzymes, glycoproteins, polyunsaturated fatty acids, sulfolipids, phenolics, terpenoids, peptides, and other secondary metabolites that exhibit antioxidant, anti-inflammatory, immunomodulatory, and anti-cancer activities [8].

Macroalgae compounds extraction uses different types of solvents: acetone, water, methanol, n-hexane, and chloroform (Table 1). These extractions are based on the principle of solvent extraction – using a liquid (solvent) to dissolve (solvate) a target molecule or group of compounds, separating the desired natural compounds from the raw material [51,52]. The extraction process has four stages: (1) penetration of the solvent into the solid matrix; (2) dissolution of the solute on the solvent; (3) diffusion of the solute from the solid matrix; (4) collection, an eventual concentration, of the extracted solute [51,53]. For the process of solvent extraction, several aspects need to be considered, such as: the solvent properties, the particle size of raw materials, temperature, extraction duration, among others, to maximize the extraction efficacy [52]. Furthermore, the extraction process results in a mixture of different types of compounds [54]. Some of the studies herein presented include purification methods such as ion exchange chromatography (a process that relies on the affinity of ion exchangers to perform the separation of ions and polar molecules) which further isolate individual compounds from the main algae extract [55]. Table 1 summarizes the studies published in the last 5 years, which will be discussed in the following subsections.

Brown macroalgae

Of the three major groups of macroalgae, brown algae are the most studied for cancer therapy [19]. This marine resource is rich in sulfated polysaccharides and other secondary metabolites like fucoxanthin, phlorotannins, and fucoidans, which have revealed promising results against several types of cancer [19,56–58]. Fucoidan has been extensively studied [19,56–58]. Geisen et al. explored the effects of a purified acetonic extract of *Fucus vesiculosus*, a Baltic brown seaweed, on PANC-1: PancTu1, Panc89, and Colo357 human PC cell lines [21]. This extract led to reduced viability, corroborated by cell cycle inhibition of proliferating cells [21]. On the other hand, *F. vesiculosus* extract presented low cytotoxic activity against terminally differentiated cells, like erythrocytes and non-malignant resting T cells, which demonstrates that proliferation is a pre-requisite for the effectiveness of the macroalgae extract [21]. As

Table 1. Anti-cancer potential of brown, red, and green macroalgae.

Macroalgae	Cancer type	Specimen (compound)	Research model	Concentration and duration	Results	References
Brown macroalgae	Pancreatic	*Fucus vesiculosus* (purified acetonic extract)	*In vitro*: PANC-1, PancTu1, Panc89, Colo357	Up to 72 h EC50 determination for each pancreatic cell line	Strong inhibition of viability due to upregulation of cell cycle inhibitors with cells dying in a Cas-independent manner. Low cytotoxicity against terminally differentiated cells and non-malignant resting T cells. Accelerated apoptotic effects in combination with inhibitors of autophagy.	Geisen et al. [21]
		Turbinaria conoides (fucoidan, water extract)	*In vitro*: MiaPaCa-2, PANC-1	6.25, 12.5, 25, 50, 100 µg/mL for 24, 48, and 72 h	At lower concentrations than 100 µg/mL: significant inhibition of cell proliferation and induction of apoptosis as well as angiogenic potential. MMP-2 and -9 activities inhibition. At 100 µg/mL: induction of cytotoxicity in both cell lines increases with time in culture.	Delma et al. [22]
			In vitro: PANC-1, MiaPaCa-2, Panc-3.27, BxPC-3	3.125, 6.25, 12.5, 25, and 50 µg/mL for 24 and 72 h	Consistent and significant dose-dependent inhibition of cell survival, with maximal inhibition at 50 µg/mL. Induction of apoptosis, activation of Cas-3, -8, and -9, and cleavage of PARP. Inhibition of 57 and 38 pathway molecules with fucoidan-F5 in MiaPaCa-2 and PANC-1 cells, respectively. Fucoidans may target p53–NFκB crosstalk and dictate apoptosis in pancreatic cancer cells.	Delma et al. [23]
		Ecklonia cava (dieckol, commercial Sigma-Aldrich, St. Louis, MO)	*In vitro*: PANC-1	0, 5, 10, 15, 20, 25, and 30 µM/mL for 24 h	Induction of apoptosis and increased ROS levels. Decreased expression of tumor cell progression inducers (cyclin D1 and PCNA). Decreased expression of Bcl-2 family proteins. Reduction of the antioxidant defense system in cancer cells without increasing inflammatory cytokine levels.	Xu et al. [24]
	Lung	*Ecklonia cava* (dieckol, commercial AKos Consulting & Solutions, Steinen, Germany)	*In vitro*: A549	25 and 50 µg/mL for 24 h	Inhibition of invasive and migratory properties of A549 cells. Induction of apoptosis via Pi3K/AKT/mTOR inhibition signaling. Tumor suppressor protein E-cadherin activation.	Wang et al. [25]
		Ecklodia Cava (fucosterol, commercial Sigma-Aldrich, St. Louis, MO)	*In vitro:* HCC827, A549, SK-LU-1, A427	0, 1.55, 3.12, 6.25, 12.5, 25, 50, and 100 µM for 24 h	Growth inhibition is more effective against A549 and SK-LU-1 cells. Induction of apoptosis and cell cycle arrest of A549 and SK-LU-1 cells.	Mao et al. [26]
		Sargassum crassifolium (native and degraded fucoidans, water extract)	*In vitro:* A549	0, 50, 100, 200, 300, 400, and 500 µg/mL for 48 h	Induction of apoptosis by native and degraded fucoidans. Decreased Bcl-2 expression, loss of mitochondrial membrane potential, increased CYC release, active Cas-9 and -3, and late apoptosis were observed. The signaling pathway mTOR is involved in native fucoidan and respective degradation products induced apoptosis of A549 cells.	Wu et al. [27]

(*continued*)

Table 1. Continued.

Macroalgae	Cancer type	Specimen (compound)	Research model	Concentration and duration	Results	References
Brown macroalgae		*Sargassum aquifolium* (oversulfated fucoidans)	*In vitro:* A549	200 µg/mL for 48 h	Fucoidan oversulfation leads to improved apoptosis of lung cancer cells. Sulfate content appears to play a key role in apoptotic cell death. Akt/mTOR/S6 pathway could be related to fucoidans induced apoptosis.	Hsiao et al. [28]
		Fucus vesiculosus and *Laminaria japonica* (fucoidan, commercial Sigma-Aldrich, St. Louis, MO)	*In vitro:* A549, CL1-5 *In vivo:* Oral administration to healthy mice for 14 days. LLC1-xenograft mouse model orally fed with fucoidan for 3 weeks	200 and 400 µg/mL for 48 h 24 mg/kg/daily for 14 days	Induction of endoplasmic reticulum stress response by activation of PERK–ATF4–CHOP pathway, leading to apoptotic cell death *in vivo* and *in vitro*. Prevention of tumorigenesis and tumor size reduction *in vivo*.	Hsu et al. [29]
		Unspecified Brown Algae (alginic acid, commercial Sigma-Aldrich, St. Louis, MO)	*In vitro*: A549, H1155	0.0, 0.2, 0.5, and 1.0 µg/mL for 48 h	*In vitro* inhibition of non-small cell lung cancer-induced angiogenesis. Downregulation of VEGF-A expression in a dose-dependent manner.	Wang et al. [30]
			In vivo: BALB/c xenograft mouse model	100 mg/kg body weight for 19 days.	Attenuated non-small cell lung cancer-induced angiogenesis *in vivo* via miR-506/STAT3/VEGF-A axis.	
	Leukemia	*Sargassum thunbergia* (halosmysin A, ethanolic extract)	*In vitro:* P388, HL-60, L1210	2, 20, and 200 M for 72 h	Strong cytotoxicity against all leukemia cell lines, with IC_{50} values ranging from 2.2 ± 3.1 to 11.7 ± 2.8 µM for P388, HL-60, and L1210 cell lines, respectively.	Yamada et al. [31]
	Leukemia Breast	*Sargassum polycystum* (fucoidan, enzymatic extract)	*In vitro:* HL-60, MCF-7	12.5, 25, 50, and 100 µg/mL for 24 h	Antiproliferative effect on both tested cell lines. Increased DNA damage, apoptotic body formation, and arrested cell cycle of both cell lines. Effects proceed via the mitochondria-mediated apoptosis pathway.	Priyan et al. [32]
	Breast	*Undaria pinnatifida* (fucoxanthin, commercial Wuhan Heli)	*In vitro:* HLEC, MDA-MB-231 *In vivo:* MDA-MB-231 xenograft mouse model	25, 50, and 100 µmol/L for 12, 24, or 48 h 100 and 500 µmol/L injected at the tumor periphery every day, for 26 days	Inhibition of growth, proliferation, migration, tube formation, and suppression of PI3K/Akt/NF-κB signaling of HLEC. Decrease of migration, invasion, and secretion of VEGF-C of MDA-MB-231. Inhibition of tumor-induced lymphangiogenesis *in vitro*. Inhibition of tumor growth and lymphangiogenesis.	Wang et al. [33]
		Undaria pinnatifida (fucoidan, Maritech extraction process)	*Clinical trial*: Co-administration of fucoidan with letrozole and tamoxifen (used hormonal therapies), breast cancer patients	500 mg twice daily for 3 weeks	No significant changes in the pharmacokinetics of letrozole, tamoxifen, or tamoxifen metabolites after co-administration with fucoidan were observed. No adverse effects or toxicity of fucoidan intake were reported. Fucoidan could be taken concomitantly with letrozole and tamoxifen without risk of significant clinical interactions.	Tocaciu et al. [34]

(*continued*)

Table 1. Continued.

Macroalgae	Cancer type	Specimen (compound)	Research model	Concentration and duration	Results	References
Brown macroalgae		*Bifurcaria bifurcata* (oxygenated acyclic diterpenes, n-hexanes and chloroform subextracts)	*In vitro*: MDA-MB-231	0–100 µg/mL for 72 h to determine the IC_{50} values	Moderate inhibition of MDA-MB-231 cells growth with IC_{50} values ranging from 11.6 to 32.0 µg/mL.	Smyrniotopoulos et al. [35]
	Cervical, colorectal, breast	*Halopteris scoparia* (n-hexane, chloroform, and methanol extracts)	*In vitro*: HeLa, CaCo-2, and MCF-7	0.5, 5, and 50 µg/mL of each extract for 48 h	Reduction in cell viability, especially against cervical adenocarcinoma cells (HeLa). Increased expression of many pro-apoptotic genes in both Cas-dependent and Cas-independent intrinsic and extrinsic pathways increased.	Güner et al. [36]
			In vivo: LD50 acute toxicity test (competent mice) and HET-CAM assay	LD50 acute toxicity test: a limit dose of 2000 mg/kg body weight HET-CAM: 0.5 and 1 mg/mL	No irritation or toxicity was observed for any extract.	
	Colorectal	*Eisenia bicyclis* (phlorofucofuroeckol A, methanol extract)	*In vitro*: HCT116, SW480, LoVo, HT-29	0, 50, and 100 µM for 24 h	Increased concentrations of phlorofucofuroeckol A induced reduction of cell viability in all tested cell lines via ATF3-mediated pathway, which may be explained by the apoptosis through the cleavage level of PARP (a biomarker of apoptosis and apoptosis-dependent cell death) increased by phlorofucofuroeckol A treatment.	Eo et al. [37]
		Costaria costata (phlorethols fraction)	*In vitro*: normal and X-ray irradiated HCT116, HT-29	0–1000 µg/mL for 24 h – cell viability Determination of the sensitivity of the cells to radiation (X-ray at a dose rate from 2 to 10 Gy) Determination of the radiosensitizing activity of phlorethols on irradiated cells	Cytotoxic activity against HT-29 (IC_{50} =92 µg/mL) and HCT116 (IC_{50}=94 µg/mL) cells. The non-toxic concentration of phlorethols lead to the inhibition of colony formation in colon cancer cells and enhanced their sensitivity to low non-toxic X-ray irradiation, which may indicate a beneficial combination of radiation and phlorethols.	Malyarenko et al. [38]
		Fucus vesiculosus (fucoidan, commercial Sigma-Aldrich, St. Louis, MO)	*In vitro*: $p53^{+/+}$ and $p53^{-/-}$ HCT116	0, 10, 25, 50, 100, and 150 µg/mL for 48 h – cell viability	Concentrations of 150 µg/mL were considered less cytotoxic for both wild type and null cells. At this concentration, fucoidan induced apoptosis, cell damage, and induced G1 arrest in cell cycle progression.	Park et al. [39]
Brown macroalgae	Liver	*Sargassum fusiforme* (SFPS, water extract)	*In vitro:* HepG2	125, 250, 500, 1000, and 2000 mg/mL for 24, 48, and 72 h – cytotoxicity and apoptosis assays	Induced high dose dependent cytotoxicity to HepG2 cells *in vitro* and stimulated apoptosis of HepG2 cells, increased the expression of Bax, and decreased the expression of Bcl-2.	Fan et al. [40]
		Ecklonia cava (dieckol, commercial LESEN Phytochem &	*In vivo:* HCC model – induced in male Wistar rats by	Oral administration of 10, 20, and 40 mg/kg	Administration of 40 mg/kg body weight was highly effective in comparison with smaller doses. It significantly reversed the activities	Sadeeshkumar et al. [41]

(*continued*)

Table 1. Continued.

Macroalgae	Cancer type	Specimen (compound)	Research model	Concentration and duration	Results	References
		Herbs Extract Solution Provider)	drinking water with 0.01 % of NDEA for 15 weeks	body weight for 15 weeks	of hepatic marker enzymes, decreased lipid peroxidative markers, increased antioxidant cascade, and decreased NDEA concentration in the liver.	
		Sargassum (fucoidan, commercial Shaanxi Kang Yue Biological Technology, Xi'an, China)	*In vitro:* SMMC-7721, Huh7 and HCCLM3	0, 10, 20, 30, and 40 mg/mL for 24, 48, and 72 h – Migration, invasion, and wound healing assays	Dose-dependent inhibition of migration and invasion for the three tested cancer cell lines. Fucoidan prevents invadopodia formation in a dose-dependent manner by deactivating the integrin αVβ3/SRC/E2F1 signaling pathway.	Pan et al. [42]
			In vivo: HCCLM3 xenograft mouse model	Oral administration with 1 g/kg for 21 days.	Reduction of tumor size and decrease of the number of liver metastasis.	
Green macroalgae	Lung	*Caulerpa taxifolia* (for synthesis of Ag NPs)	*In vitro* – A549	10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 mg/mL overnight	Biosynthesized Ag NPs exhibited cytotoxicity against A549 cells, with an IC_{50} of 40 mg/mL. Cell morphology was affected.	Zhang et al. [43]
	Breast	*Chaetomorpha sp.* (ethanol and aqueous extracts)	*In vitro* – MCF-7, MDA-MB-231	20–200 µg/mL for 72 h – cell viability	Ethanol extract of algae possessed higher antioxidant and anti-cancer activity compared to aqueous extract. MDA-MB-231 breast cancer cell lines were significantly affected by different concentrations of ethanol extracts of *Chaetomorpha sp.*	Haq et al. [44]
	Liver Breast	*Ulva lactuca* (phycocyanin, methanolic extract)	*In vitro* – HepG2, MCF-7	10, 20, and 40 µM – cell viability and apoptosis assays	Antiproliferative and pro-apoptotic activities on liver and breast cancer cell lines.	Al-Malki [45]
	Liver	*Ulva lactuca* (sulfated polysaccharides and aqueous extract)	*In vivo*: Hepatocarcinogenesis induced by injection of DENA in rats	Oral administration of 50 mg/kg daily for 2, 12, and 24 weeks	Marked chemoprevention of DENA-initiated hepatocarcinogenesis through inhibition of abnormal cell proliferation and induction of apoptosis. Modest inhibition of rat liver carcinogenesis was observed with the aqueous extract. Sulfated polysaccharides changed serum parameters of hepatic damage and modulated various components of the hepatic enzymatic and nonenzymatic antioxidant defense systems.	Hussein et al. [46]
Red macroalgae	Breast	*Kappaphycus alvarezii* (methanolic extract)	*In vitro:* MCF-7	1, 3, 7, 9, 12, and 15 mg/mL for 24 h – cell viability	Induction of cytotoxicity on MCF-7 cell line, with an IC_{50} value of 4.1 mg/mL.	Chang et al. [47]
			In vivo: Subchronic toxicity in healthy rats and mammary carcinogenesis induced by DMB rat model	Oral administration 2000 mg/kg body weight) daily – toxicity for 8 weeks Oral administration of 300 mg/kg for 11 weeks	No toxicity was observed for the sub-chronic toxicity test. Decreased the size of the tumors and the white blood cell level.	
		Porphyridium sordidum (polysaccharides)	*In vitro* – Normal and electroporated MCF-7 and MDA-MB-231	10, 25, 50, 75, or 100 µg/mL for 48 h	Cell survival appeared to be dose and cell type dependent. Additional application of electroporation (200 V/cm) increased the effect of polysaccharide on cell	Nikolova et al. [48]

(*continued*)

Table 1. Continued.

Macroalgae	Cancer type	Specimen (compound)	Research model	Concentration and duration	Results	References
					proliferation: 75 µg/mL polysaccharide +200 V/cm electroporation led to a 40% decrease in viability and changes in cell morphology.	
	Lung	*Gelidiella acerosa* (sequential extraction)	*In vitro:* A549	0.1–2 mg/mL for 24 h – cell viability and apoptotic assays	Inhibition of cell proliferation, migration, and colonization as well as induction of apoptosis.	Fazeela Mahaboob Begum et al. [49]
	Lung Gastric Melanoma	*Gracilariopsis lemaneiformis* (polysaccharides, water extract)	*In vitro*: A549, MKN28, and B16	5, 10, 20, 30, 40, 50, 60, 80, or 100 µg/mL for 24, 48, and 72 h – cell viability and apoptotic assays	Modulation of cell viability, apoptosis, morphology, and related Fas/FasL signaling pathway. Inhibition of cell proliferation by induction of apoptosis for all three tested cell lines.	Kang et al. [50]
			In vivo: A549-xenograft mouse model	Intraperitoneal injection at 20, 40, and 80 mg/kg body weight twice a week for 6 weeks.	Growth inhibition of xenografted tumors in mice in a concentration-dependent manner. The presence of cleaved Cas-3 and Ki67 are important indicators of apoptosis and proliferation, respectively.	
			In vivo: HepG2-xenograft mouse model	Orally fed with SPFS 100, 200, and 400 mg/kg body weight for 28 days	Inhibition of tumor growth and induction of immunomodulatory activity *in vivo*.	
			In vivo: adult male zebrafish model	Oral administration 15, 30, 45, and 60 µg/day for 10 days – *Acute and chronic toxicity analysis in zebrafish*	Inhibition of tumor growth in zebrafish.	

PANC-1: human pancreatic cancer cell line from pancreatic ductal adenocarcinoma; **PancTu1:** human pancreatic cancer cell line from pancreatic ductal adenocarcinoma; **Panc89:** human pancreatic cancer cell line from ductal adenocarcinoma derived from metastatic site – lymph node; **Colo357:** human pancreatic cancer cell line from metastatic pancreatic adenocarcinoma; **MiaPaCa-2:** human pancreatic cancer cell line from pancreatic ductal adenocarcinoma; **Panc-3.27:** human pancreatic cancer cell line from pancreatic adenocarcinoma; **BxPC-3:** human pancreatic cancer cell line from pancreatic ductal adenocarcinoma; **A549:** human lung cancer cell line from lung adenocarcinoma; **HCC827:** human lung cancer cell line from lung adenocarcinoma; **SK-LU-1:** human lung cancer cell line from lung adenocarcinoma; **A427:** human lung cancer cell line from lung adenocarcinoma; **CL1-5:** human lung cancer cell line from lung adenocarcinoma; **P388:** Leukemia cancer cell line from mouse lymphoma; **HL-60:** human leukemia cancer cell line from adult acute myeloid leukemia; **L1210:** cancer cell line from mouse leukemia; **MCF-7:** human breast cancer cell line from invasive breast carcinoma of no special type; derived from metastatic site – pleural effusion; **HLEC:** human lymphatic endothelial cells; **MDA-MB-231:** human breast cancer cell line from breast adenocarcinoma; derived from metastatic site – pleural effusion; **HeLa:** human cancer cell line from papillomavirus-related endocervical adenocarcinoma; **CaCo-2:** human cancer cell line from colon adenocarcinoma; **HCT116:** human colorectal cancer cell line from colon carcinoma; **SW480:** human colorectal cancer cell line from colon adenocarcinoma; **LoVo:** human colorectal cancer cell line from colon adenocarcinoma; derived from metastatic site – left supraclavicular lymph node; **HT-29:** human colorectal cancer cell line from colon adenocarcinoma; **HepG2:** human liver cancer cell line from hepatoblastoma; **SMMC-7721:** human cancer cell line from papillomavirus-related endocervical adenocarcinoma; **Huh7:** human liver cancer cell line from hepatocellular carcinoma; **HCCLM3:** human liver cancer cell line from hepatocellular carcinoma; **MKN28:** human gastric cancer cell line from gastric tubular adenocarcinoma; derived from metastatic site-liver; **B16:** mouse melanoma cancer cell line; **MMP:** matrix metalloproteases; **Cas**: caspase; **NFκB:** nuclear factor κB; **Bcl-2:** B-cell leukemia-2; **PARP:** poly ADP ribose polymerase; **ROS:** reactive oxygen species; **Pi3K/AKT/mTOR pathway**: plays a key role in lung cancer cell survival, proliferation, and growth; **mTOR:** Akt/mammalian target of rapamycin pathway – related to several cell functions such as invasion, proliferation, migration, and survival; **PERK–ATF4–CHOP pathway:** plays a key role in inducing CHOP transcription; **CYC:** cytochrome C; **Bax:** Bcl-2 associated X protein; **DENA:** diethylnitrosamine; IC_{50}**:** the effective dose of the substance required to inhibit cell growth by 50%; **HET-CAM:** Hen's egg test chorioallantoic membrane; **LD50:** determination the lethal dose of a substance that will kill 50% of the tested animals; **SFPS:** *Sargassum fusiforme* polysaccharide; **HCC:** hepatocellular carcinoma; **NDEA:** N-nitrosodiethylamine.

highlighted by the authors, future *in vivo* studies should explore such results and the mechanisms of action over the cell cycle [21]. The effects of fucoidan isolated with water extract from *Turbinaria conoides,* macroalgae found along the south-east coast of India, was tested with Mia PaCa-2 and PANC-1 human PC cell lines, showing interesting results [22]. This fucoidan effectively inhibited cell proliferation and induced apoptotic death in both cell lines [22]. Additionally, the extract exhibited significant anti-angiogenic potential at 100 g/mL leading to complete inhibition of human aortic endothelial cell tube formation [22]. The same authors, in a recent study, characterized the active fractions of *Turbinaria conoides* fucoidan extract, exploring the mechanisms involved in its pancreatic anti-cancer activity [23]. Five fractions of fucoidan isolated by ion exchange chromatography were tested with: PANC-1, MiaPaCa-2, Panc-3.27, and BxPC-3 human PC cell lines. All fractions presented a dose and time-dependent regulation of cell survival [23]. In addition, fucoidan induced apoptosis, cleavage of poly ADP ribose polymerase (an enzyme involved in DNA repair), and activated caspases 3, 8, and 9 (each play a critical role in mediating apoptotic cell death) [23]. A specific fraction of the extract (f5) inhibited the NF-κB pathway (related to transcription of several genes associated with tumorigenesis and progression) in Mia PaCa-2 and PANC-1 cells [23]. Furthermore, fucoidan inhibited constitutive and tumor necrosis factor-α mediated NFκB DNA-binding activity in PC cells [23]. NFκB is a key player in the apoptotic resistance of PC cells, and the inhibition of this nuclear transcription factor can lead to apoptosis, sensitizing cells to chemotherapy treatments [59,60].

Dieckol, a phlorotannin polyphenolic compound present in the brown alga *Ecklodia cava*, was tested with PANC-1 cells [24]. Dieckol decreased the expression of cell progression inducers cyclin D1 and proliferating cell nuclear antigen – PCNA, the anti-apoptotic protein B-cell leukemia-2 (Bcl-2), and increased the expression of pro-apoptotic protein Bax [24]. The apoptotic effects on PC cells were related to increased levels of reactive oxygen species (ROS) [24]. In cancer cells, chemoresistance is associated with the antioxidant defense system and, as such, these anti-cancer drugs should increase ROS levels, promoting cancer cell death [24].

Dieckol extracted from *Ecklodia cava* (commercial AKos Consulting & Solutions, Steinen, Germany) was tested with human A549 lung cancer cells [25]. This compound inhibited cell migration and invasion and induced apoptosis by activating tumor suppressing E-cadherin (a glycoprotein of the adherens junctions, crucial in cell adhesion and maintenance of epithelial phenotype with major importance on epithelial–mesenchymal transition (EMT)) levels [24]. Furthermore, apoptosis was induced via inhibition of the mTOR signaling pathway [24]. This pathway regulates cellular metabolism, differentiation, and proliferation, being its activation closely related to tumor development and cancer therapy resistance [25]. Investigation toward the discovery of drugs that can inhibit the PI3K signaling cascade is needed [25,61]. In this sense, dieckol presents great potential to be considered for lung cancer therapy [25].

Fucosterol, a phytosterol that can be also found in *Ecklonia cava* or *Ecklonia stolonifera,* as well as in other plant species, was evaluated as a possible anti-cancer compound for lung cancer [26]. It was effective against A549 and SK-LU-1 lung cancer cell growth and invasion, by inducing apoptosis and cell cycle arrest [26]. In addition, this compound inhibited the growth of A549-xenografted tumors in mice in increasing doses (intraperitoneal administration at 20, 40, and 80 mg/kg body weight twice a week for 6 weeks), making it a promising candidate for lung cancer therapy [26].

Wu et al. tested the effects of a native and three degraded fucoidans by extrusion (a bioreaction process of short duration that involves heating, mixing, shearing, pressurizing, and shaping, to increase the extraction yield of fucoidan) from *Sargassum crassifolium* with A549 cells [27]. The chemical compositions among the different fucoidans varied, though the structural features were similar [27]. All types of fucoidan promoted apoptosis of A549 cells, by observation of mitochondrial membrane potential loss, an increase of cytochrome c release, activation of caspases 9 and F3, and decrease of Bcl-2 expression [27]. In addition, the authors concluded that mTOR (signaling pathway related to several cellular functions – proliferation, invasion, and survival, frequently activated in cancer) is involved in fucoidan induced apoptosis [27].

Fucoidan biological activity is related to molecular: weight, degree, and pattern of sulfation, and glycosidic branches [28]. As an extension of the previous work [27], Hsiao et al. analyzed the effect of oversulfation on fucoidan from *Sargassum aquifolium* and tested its anti-cancer activity on A549 cells [27,28]. The authors concluded that fucoidan with increased sulfate content induced more apoptosis of lung cancer cells and that the mTOR pathway was involved [28].

Hsu et al. explored for the first time the effects of fucoidan over cell apoptosis via endoplasmic reticulum stress studies [29]. The endoplasmic reticulum is an intracellular organelle with important functions, such as: lipid biogenesis, maintenance of Ca^{2+} homeostasis, and protein folding, and its stress-induced apoptosis is

related to several pathologies, including cancer [29]. The authors analyzed the effects of fucoidan *in vitro* (A549 and CL1-5 lung cancer cell lines treated with 200 and 400 μg/mL of fucoidan for 48h) and *in vivo* (lung cancer murine LLC1-xenograft model orally fed with fucoidan for 3 weeks) and found that fucoidan activated one of the major pathways in endoplasmic reticulum stress-mediated apoptosis – PERK–ATF4–CHOP, which conducted to apoptotic cell death *in vitro* and tumor reduction *in vivo* [29].

Alginic acid is a natural polyuronic acid very common in edible brown algae. This compound possesses anti-inflammatory properties [30]. Wang et al. explored the effects of alginic acid *in vitro* on A549 and H1155 lung cancer cells and *in vivo* on an A549-xenograft mouse cancer model orally fed with 100 mg/kg body weight of alginic acid for 19 days [30]. The authors focused on lung cancer-driven angiogenesis and analyzed the expression of VEGF-A (angiogenesis promoter), and found that alginic acid downregulated VEGF-A expression [30].

Leukemia is the common terminology to classify a group of malignant disorders related to an increased number of leucocytes in the bone marrow and/or blood [62]. Halosmysin A, a metabolite isolated from the marine brown algae *Sargassum thunbergia* was tested with murine P388 and L1210, and human HL-60 leukemic cell lines, showing high cytotoxicity [31]. Future investigations should address the structure–activity relationship of this compound to elucidate the mechanisms and specific molecular pathways underlying its action [31]. Fucoidan from *Sargassum polycystum* was extracted using an enzyme (cellulase), purified by anion exchange chromatography, and evaluated with HL-60 leukemia and MCF-7 breast cancer cells [32]. The authors observed that this fucoidan exhibited anti-proliferative effects via mitochondria-mediated apoptosis (one of the main pathways for apoptosis, frequently inactivated in cancer cells), increasing DNA damage and apoptotic body formation [32,63]. The carotenoid fucoxanthin extracted from *Undaria pinnatifida* was evaluated with human lymphatic endothelial cells (LEC) and MDA-MB-231 breast cancer cells [33]. Fucoxanthin inhibited the migration, proliferation, and formation of tube-like structures by human LEC [33]. This phenomenon is important, once the proliferation and migration of LEC in lymphatic vessels surrounding the tumor (tumor-related lymphangiogenesis) diminish the growth of the tumor [33]. Furthermore, these results were corroborated *in vivo* in mice MDA-MB-231 derived tumors and treated daily for 26 days with fucoxanthin 100 and 500 μmol/L injected at the tumor periphery. It was observed a decrease in tumor growth and lymph tube density [33]. In a clinical trial setting, Tocaciu et al. explored the effects of fucoidan extracted from *Undaria pinnatifida* on the pharmacokinetics of two drugs commonly used for breast cancer therapy – letrozole and tamoxifen [34]. The breast cancer patients were divided into two groups: tamoxifen or letrozole and taken 500 mg of fucoidan orally twice a day. Relevant parameters (letrozole, tamoxifen, 4-hydroxytamoxifen, and endoxifen) were measured at baseline and after fucoidan administration, through plasma concentration [34]. Fucoidan did not affect plasma concentrations of the drugs, nor its metabolites, presenting no adverse effects or toxicity [34]. Future studies should address the possible fucoidan concomitant administration with pharmaceuticals on other types of cancer.

Smyrniotopoulos et al. studied the effects of oxygenated acyclic diterpenes isolated from the Irish brown algae *Bifurcaria bifurcata* over MDA-MB-231 cells [35]. The authors isolated eight different compounds – six new and two known acyclic diterpenes – eleganediol and bifurcane [35]. Only three of the tested oxygenated acyclic diterpenes, one new, C20H32O3, and the two known, presented anti-cancer activity by reducing MDA-MB-231 cell viability [35]. The effects of methanol, chloroform, and n-hexane derived extracts from macroalgae *Halopteris scoparia* were tested with HeLa (cervical), CaCo-2 (colorectal), and MCF7 (breast) cell lines by Güner et al. [36]. All extracts reduced cell viability with more pronounced effects on HeLa cells [36]. In addition, the expression of pro-apoptotic genes in caspase pathways increased [36]. Moreover, no toxicity was observed *in vivo* in mice fed with 2000 mg/kg body weight of *Halopteris scoparia* extracts, which reinforces the potential of *Halopteris scoparia* extracts to be incorporated in pharmaceuticals aiming at human cancer therapy [36]. Eo et al. explored the molecular mechanism of phlorofucofuroeckol A, a phlorotannin isolated from *Eisenia bicyclis* in colorectal cancer [37]. Phlorofucofuroeckol A induced apoptosis and decreased cell viability of human colorectal cancer cells (HCT116, SW480, LoVo, and HT-29) via ATF3-mediated pathway (ATF3 is a master regulator of metabolic homeostasis, directly influencing cancer proliferation) [37,64].

Radiotherapy is one of the most effective treatments for cancer [38,65]. It relies on the use of radiation to kill cancer cells and diminish tumor size [65]. However, increasing radiation therapy doses lead to severe damage to healthy cells [38,65]. One option to boost radiotherapy is to augment the radiosensitivity of cancer cells, and that premise was tested by Malyarenko et al.

on colon cancer [38]. The authors studied the effects of phlorethols from *Costaria costata,* a brown macroalga, on HT-29 and HCT 116 cells [38]. These compounds exerted cytotoxic activity and enhanced cell sensitivity to non-toxic low X-ray irradiation doses [38]. Furthermore, the combination of phlorethols with radiation led to a synergistic effect – the treatment with X-ray (2 Gy) and phlorethols at 5, 10, and 20 μg/mL led to colony formation inhibition of HT-29 by 28%, 39%, and 41%, and of HTC 116 by 15%, 24%, and 40%, respectively, in comparison to irradiated cells (doses of 2, 4, 8, and 10 Gy lead to inhibition of the colonies number of HT-29 by 26%, 55%, 95%, and 97% AND HCT 116 by 18%, 30%, 47%, and 61%, respectively) [38]. Park et al. aimed to investigate the anti-cancer effect of fucoidan on two p53 isogenic HCT116 cells (one without the gene p53 and the wild-type with the gene p53) and concluded that regard from the p53 status, fucoidan presents the capacity to induce apoptosis, inhibit cell viability and lead to DNA damage in similar proportions for both cell lines [39]. The gene p53 is a transcription factor with pro-apoptotic functions that is absent in most tumor cells [66].

Liver cancer ranks number three as the deadliest cancer [40]. Fan et al. investigated the therapeutic potential of *Sargassum fusiforme* extracts for this type of cancer [40]. An *in vivo* HepG2 xenograft mouse model was orally administrated with *Sargassum fusiforme* extract at 100, 200, and 400 mg/kg body weight for 28 days. The authors concluded that the extract inhibited cell growth and increased NO, IgM, TNF-α, and IL-1 levels [40]. Furthermore, an increase of *Bax* and a decrease in *Bcl-2* expression were detected, which led to the inhibition of tumor progression [40].

Dieckol from *Ecklodia Cava*, a compound previously cited in this review for its potential therapeutical application on pancreatic and lung cancer [24,25], was also tested in liver cancer [41]. An *in vivo* rat hepatocarcinogenesis model (liver cancer induced in rats by ingestion of 0.01% of N-nitrosodiethylamine (NDEA) through drinking water for 15 weeks) was used [41]. Dieckol orally administrated at 40 mg/kg body weight for 15 weeks: decreased lipid peroxidative markers, increased antioxidant cascade, reversed hepatic marker enzymes activity, and decreased NDEA concentration [41]. Oxidative damage is closely related to chronic inflammation and liver cancer, and lipid peroxidation plays a key role in carcinogenesis leading to the production of toxic products that can attack cellular targets [41,67]. Since dieckol decreased lipid peroxidative markers and NDEA concentration in the liver, it seems to be a promising candidate to target liver cancer [41].

Pan et al. explored the effects of fucoidan extracted from *Sargassum* brown macroalgae on *in vitro* and *in vivo* models of liver cancer [42]. Fucoidan was tested for 24 h, 48 h, and 72 h with concentrations of 10, 20, 30, and 40 mg/mL and this compound was able to reduce the migration and invasion in a dose-dependent manner of SMMC-7721, Huh7, and HCCLM3 liver cancer cell lines [42]. Furthermore, decreased expression of several invadopodium-related proteins (Src, Cortactin, N-WASP, ARP3, CDC42, MMP2, MT1-MMP, integrin Av, and β3) was detected in the HCCLM3 cells as well as increased levels of several endoplasmic reticulum-related proteins (GRP78, IRE1, SPARC, integrin α1, and β1) [42]. The *in vivo* mouse model (HCCLM3 xenograft mice liver cancer model) supplemented with 1 g/kg body weight for 21 days, presented decreased liver tumor size and 40% less occurrence of lung cancer metastasis [42].

Green macroalgae

Green macroalgae show a tremendously wide variability of size, shape, and habit, being the most heterogeneous group of photoautotrophic protists on earth [68]. At least 7000 species are known, being the most diverse of the algal groups [69]. This type of algae can be found on all continents and curiously, the earliest evidence of green algae species comes from fossils a billion years old [69]. Regarding green algae compounds, sulfated polysaccharides, sulfolipids, glycolipids, among others, have been exhibiting potential against cancer [68]. One such example is biosynthesized silver nanoparticles (Ag NPs) using the algae *Caulerpa taxifolia* (obtained by mixing HPLC purified algae extract with Ag NO3 aqueous extract) against A549 cells [43]. At a dose of 40 mg/mL, this compound showed cytotoxicity and cell morphology damage [43]. Haq et al. tested the anti-cancer activity of *Chaetomorpha sp.* ethanolic and aqueous extracts against MCF-7 and MDA-MB-231 cells [44]. The ethanolic extract presented pronounced anti-cancer activity by inhibiting the growth of MDA-MB-231 cells, but not in MCF-7 cells [44]. Furthermore, dichloroacetic acid, oximes, and L-α-terpineol were identified as some of the compounds present in the ethanolic extract responsible for this anti-cancer activity [44]. *Ulva lactuca* algae methanolic extract loaded on albumin nanoparticles also demonstrated anti-cancer activity against MCF7 and HepG2 cancer cells, inducing cell death by increasing of caspase 8 and 9 levels [45]. The effects of *Ulva lactuca* polysaccharide sulfate and aqueous extract against liver cancer were also tested by Hussein et al. [46]. The authors used an *in vivo* induced

hepatocarcinogenesis rat model (as in [41]) fed with 50 mg/kg daily of each extract for 2, 12, and 24 weeks [46]. Sulfated polysaccharides of this green macroalga inhibited cancer cell proliferation inducing apoptosis [46]. Furthermore, several serum parameters related to hepatic damage (AST, ALT, ALP, and γ-GT) were altered, as well as the components of hepatic non-enzymatic and enzymatic antioxidant defense systems [46]. The authors propose that sulfated polysaccharides from *U. lactuca* inhibit severe oxidative damage initiated by DENA by indirectly activating the antioxidant defense system and interacting directly with ROS [46].

Red macroalgae

Red algae or *Rhodophyta* comprises more than 5000 different species of algae [70]. Their composition is unique and most of them possess novel sulfated galactans and polysaccharides, such as carrageenans and agars, and glycoproteins, among other compounds, with scientifically documented health benefits [1,70–72]. Crude extract from *Kappaphycus alvarezii* was tested over MCF-7 cells, and given to rats (2000 mg/kg body weight for 60 days to evaluate the eventual chronic toxicity and heavy metal toxicity studies (determination of: cadmium, arsenic, chromium, iron, manganese, lead, mercury, nickel, selenium, and zinc in the liver) [47]. The authors also tested the effects of the extract on a rat mammary tumor model (induced by 65 mg/kg body weight of dimethylbenz[a]anthracene (DMBA) intake), by feeding them with 300 mg/kg for 11 weeks, after tumor development [47]. *Kappaphycus alvarezii* reduced MCF-7 cell viability from 84.91% to 0.81% [47]. For the sub-chronic and heavy metal toxicity in rats, no differences were found between the control and test groups [47]. In the mammary cancer model, the untreated group presented a significantly higher growth rate of tumors in comparison with the experimental group [47]. Nikolova et al. explored the anti-cancer potential of a new extracellular polysaccharide (composed of xylose:glucose and galactose:mannose:rhamnose in a molar ratio of 1:0.52:0.44:0.31) isolated from the red algae *Porphyridium sordidum* with MCF-7 and MDA-MB231, and concluded that after 48 h of administration, cell survival appeared to be dose and cell type dependent [48]. Furthermore, the authors administrated the red algae derived polysaccharides to cells by reversible electroporation (a method to increase the transport of compounds through the plasma membrane) and concluded that the application of 200 V/cm electroporation combined with 75 μg/mL of algae polysaccharide decreased MDA-MB231 cells viability in 40%, as well as induced cell morphology alterations [48]. Fazeela Mahaboob Begum et al. tested an extract with solvents of different polarity, rich in polyphenols and flavonoids, from the red algae *Gelidiella acerosa* against A549 cells and *in vivo* using a lung cancer zebrafish model (injection of A549 cells in the muscle to develop tumors) fed with 15, 30, 45, and 60 μg/mL daily for 10 days [49]. It also tested the acute and chronic toxicity, by feeding zebrafish with 100, 250, and 500 μg of crude extract/-day [49]. *Gelidiella acerosa* extract inhibited cell: proliferation, migration, and colonization, inducing apoptosis by activation of caspase 3 and Bax protein, with decreased expression of Bcl-2 and Bcl-XL [49]. Additionally, GSK3β was activated, PI3K/Akt was downregulated and MMP2 expression decreased *in vitro* [49]. The extract led to the inhibition of tumor growth *in vivo*, and no acute or chronic toxicity was observed [49]. The PI3K/Akt cascade is typically deregulated in lung cancer, which leads to metastasis, prolonged cell survival, and evasion of apoptosis [49]. The decreased expression of matrix metalloproteinase MMP2 (a molecule that plays a key role in tumor proliferation, growth, and invasion) indicates that the algae extract presents anti-metastatic activity [49]. In the *in vivo* model, the experimental group presented: less angiogenesis, lysing tumor cells (cancer cells die by large numbers within a short period), normal muscle pathology, and an increase in the normal cell population at a dose of 60 μg/day [49]. Polysaccharides extracted from *Gracilariopsis lemaneiformis* were tested on human A549 lung and MKN28 gastric cancer cell lines, and mouse melanoma cell line B16, by Kang et al. [50]. The authors concluded that these polysaccharides were capable of exerting anti-tumor activity by modulating cell morphology, viability, and apoptosis on all cell types [50]. Furthermore, at 30 μg/mL concentration, polysaccharides inhibited cell growth in a dose and time dependent manner, particularly over A549 cells [50] (Figure 1).

Conclusions, limitations, and future perspectives

The burden of cancer in society hungers for novel compounds that can effectively target tumors without the side effects implied by currently available therapies. Brown macroalgae have been the most widely studied type of algae with 14 species tested on at least one of these types of cancer: pancreatic, lung, breast, cervical, colorectal, and liver (Figure 2). Three species of brown algae demonstrated the potential to target three different types of cancer, showing immense biomedical potential: *F. vesiculosus, E. cava, and H. scoparia* (Figure 2).

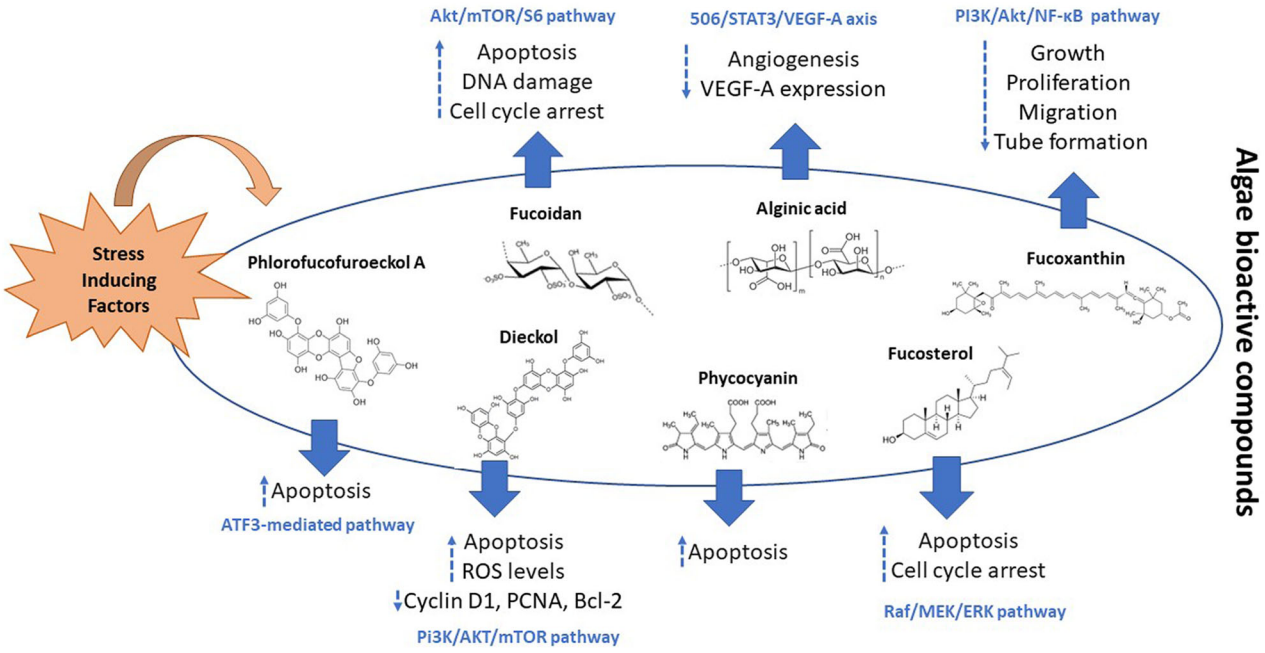

Figure 1. Mechanisms of action of macroalgae major bioactive compounds in cancer cells.

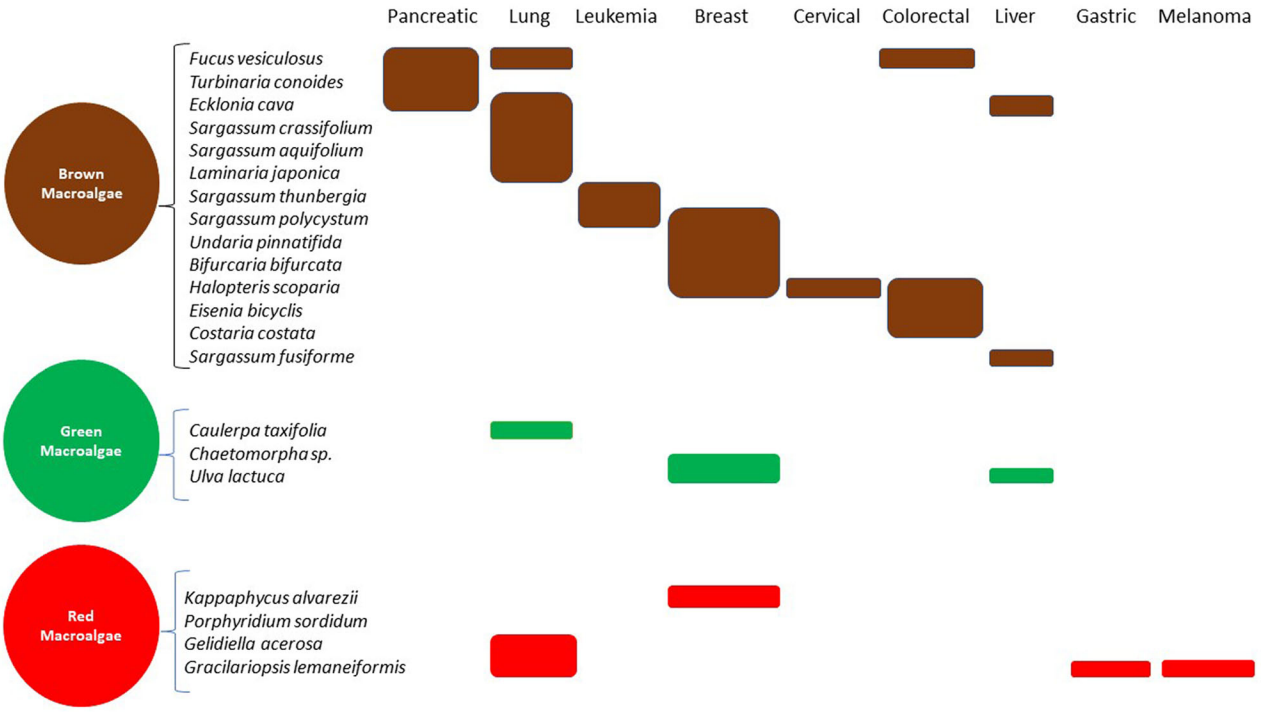

Figure 2. Brown, green, and red macroalgae species and targeted types of cancer.

About green macroalgae, three different species (*C. taxifolia*, *Chaetomorpha sp.,* and *U. lactuca*) were identified with the potential to target lung, breast, or liver cancer. *Ulva lactuca* presented anti-cancer activity for breast and liver cancer.

Similarly to the green macroalgae, red macroalgae also revealed anti-cancer potential, being worth mentioning *G. lemaneiformis,* which showed evidence to target melanoma, lung, and gastric tumors (Figure 2). In what concerns molecules with anti-cancer activity, fucoidan from brown algae has been the most widely studied. This natural compound has been widely used by biomedical and pharmaceutical industries because of its promising therapeutic properties against cancer and low toxicity. Fucoidan shows the capacity to induce cell cycle arrest and apoptosis on several cancer cell lines,

but the corresponding mechanisms of action remain uncertain. Future studies should address the discovery of these mechanisms and test the anti-cancer activity of fucoidan in more relevant cancer models, and/or in co-administration with current chemotherapeutic agents.

Most of the studies performed with macroalgae compounds/extracts are performed on *in vitro* cell and *in vivo* mouse models of cancer. *In vitro* studies are excellent to start the studies such as a preliminary functional screening, and to identify the molecular of a compound or extract. However, these assays constitute a poor predictor of therapeutic response because several processes that occur in the human body such as the interaction between nutrients/pharmaceuticals, metabolic activity, and variation in dose, among others, are not considered. On the other hand, animal studies bring to the equation some of these factors, leading to a more flexible approach for health effect studies, although, due to animals' different physiological systems, these conclusions are still limited for humans. The extraction method should be considered carefully for each macroalga to maximize the extraction of compounds with functional properties. Choosing the most appropriate extraction method will condition the recovery of the seaweed fractions which might affect further applications, including cancer.

As presented in this review, macroalgae of marine origin possess molecules that can be incorporated into the development of novel pharmaceuticals targeting several types of cancer. However, to confirm such anti-cancer activities, the promising results obtained in *in vitro* and *in vivo* studies should be tested on human subjects. Despite some advances in recent years, the literature about the anti-cancer activity of marine macroalgae remains incomplete. More studies are needed to clarify such anti-cancer activities and determine the real potential of these compounds for the development of novel pharmaceuticals.

Disclosure statement

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