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Anti-colorectal cancer effects of seaweed-derived bioactive compounds

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Seaweeds are classified as Chlorophyta, Rhodophyta, and Phaeophyta. They constitute a number of the most significant repositories of new therapeutic compounds for human use. Seaweed has been proven to possess diverse bioactive properties, which include anticancer properties. The present review focuses on colorectal cancer, which is a primary cause of cancer-related mortality in humans. In addition, it discusses various compounds derived from a series of seaweeds that have been shown to eradicate or slow the progression of cancer. Therapeutic compounds extracted from seaweed have shown activity against colorectal cancer. Furthermore, the mechanisms through which these compounds can induce apoptosis *in vitro* and *in vivo* were reviewed. This review emphasizes the potential utility of seaweeds as anticancer agents through the consideration of the capability of compounds present in seaweeds to fight against colorectal cancer.

KEYWORDS

colorectal cancer, therapeutic compounds, Chlorophyta, Rhodophyta, Phaeophyta

Introduction

Colorectal cancer (CRC) is the most common type of cancer throughout the world, accounting for approximately 10% of all new cancer cases and mortality, as projected in GLOBOCAN 2020 (1). The prevalence rates of CRC are increasing among nations with a medium human development index, such as Brazil, Russia, and countries of Latin America (2). The pathology of CRC includes carcinogenesis of the rectum, colon, appendix, and anus (3). Familial and environmental factors contribute to the risk of CRC from two well-defined causes particularly amenable to dietary influence (4). In the clinical situation, chemotherapy is a common treatment modality for CRC (5). Nevertheless, the majority of current chemotherapeutic drugs for the therapy of advanced-stage CRC, for instance cisplatin, have been repeatedly reported to elicit adverse side effects and are comparatively less effective (6). Several lines of scientific evidence, from molecular mechanisms to clinical trials, show that herbal medicines have anti-CRC potential and have been used for therapy and recovery (7).

Seaweeds have been utilized for food and medicinal herbs since ancient times in Asia (8). It has been consumed as a food for over 1,700 years, which can be dated back to Japan in the fourth century and China during sixth century. Particularly, people

living long in coastal areas frequently used seaweed as a main dish, side dish, or soup (9). Consumption of seaweed supplies sufficient macro and micronutrients, which are essential to maintaining human health (10). Besides nutritional effects, seaweed has long been adopted as a drug in Traditional East Asian Medicine to alleviate the progression of multiple cancers (11). Seaweeds as large multicellular marine organisms are classified into three major groups based on their pigments and the origin of sulfated polysaccharides: green (Chlorophyta), red (Rhodophyta), and brown (Phaeophyta) (12, 13). They represent a main source of bioactive compounds, yielding primary metabolites essential for natural growth and many secondary metabolites, which include polysaccharides, polyunsaturated fatty acids, phenolics, vitamins, pigments, minerals, terpenes, and phytosterols (14). Due to their various constituents, seaweeds have shown diverse biological activities, including anticancer activity (15).

Seaweeds have long been recognized as a therapeutic option of cancer (16). Accumulating evidence advocates that the anticancer effects of bioactive ingredients extracted from seaweed are produced *via* multiple mechanisms of action, including inhibition of growth, invasion, and metastasis of cancer cells, and through the stimulation of apoptosis in cancer cells (17). Among the East Asian population, people who regularly consumed seaweed reduced their risk of CRC development by half (10). Several researches have suggested that CRC can be effectively treated with marine natural products (18). According to one such report, brown seaweed *Turbinaria decurrens* has the potential as an anti-CRC agent (19). The highly cytotoxic and antiproliferative activities of seaweeds from the Portuguese coast have been proven in a model of Caco-2 CRC cells *in vitro* (20). *Sargassum oligocystom* significantly decreased cell viability in SW742, HT-29, WiDr, and CT-26 CRC cells through activation of the APC gene (21). Although several studies have reported the therapeutic properties of seaweed in CRC, its mechanism of action and active ingredients are still unclear and unclassified. In this review, we summarize the various effects of diverse compounds derived from seaweed on CRC.

Categorization of anti-CRC compounds isolated from seaweeds

Polysaccharides

The polysaccharides present in seaweeds are many and diverse (22). They are hydrophilic molecules with high solubility in water and a repeating structure (23). The polysaccharides in seaweed are divided into sulfated (fucoidan, carrageenan, and ulvan) and non-sulfated (agarose and laminarin) (24). Chlorophyta, Phaeophyta, and Rhodophyta contain polysaccharides of varied chemical composition and structure (25).

Previous studies suggested that polysaccharides from seaweed showed strong anti-CRC and preventive activities. They can either directly inhibit cancer cells or affect various phases of carcinogenesis and the progression of tumor through the regulation of the balance between proliferation and programmed cell death and can also be potentially used for cancer prophylaxis (26). Three polysaccharide fractions isolated from *Porphyra haitanensis* exerted inhibitory effects on growth in the HT-29, LoVo, and SW-480 colon cancer cell lines (27). Other active components contained in seaweed that exhibit similar effects against CRC are shown in Table 1. Another study reported on an evaluation of the anti-CRC activity of sulfated glucuronorhamnoxylan polysaccharides from *Capsosiphon fulvescens* (28). Polysaccharides from *Jania rubens* upregulated the gene expression of Bax, caspase 8, and P53 in human colon cancer Caco-2 cells (29). A summary of mechanisms for other active components from seaweed on anti-CRC is shown in Table 2.

Agarose

Red algae cell walls mainly consist of agarose which is composed of alternative units of D-galactose and 3,6-anhydro-L-galactose (AHG) linked by alternating α-1,3- and β-1,4-glycosidic bonds (62). After being consumed, agarose is digested, fermented, and metabolized by intestinal microbiota in the human large intestine, which makes it unique among red algal polysaccharides (63). Clinical trials have suggested that people in Asia who regularly consume red seaweeds are at a lower risk of CRC, which is relevant to their daily intake of seaweeds (64). It is speculated that this effect may be related to biologically active agarose components enriched from red seaweed. Upregulation of caspase-3, Bax, and caspase-9 expression and downregulation of Bcl-2 and Bcl-xL were observed in HCT-116 cells after AHG treatment (30). Therefore, the growth of human colon cancer HCT-116 cells was effectively suppressed by AHG, indicating that AHG is a potential alternative as an anti-CRC agent.

Ulvan

The sulfated polysaccharide known as "ulvan" is extracted from green algae of the ulva species (35). Ulvan mainly consists of cellulose, xyloglucan, and glucuronan with various other types of sugars (65). It is reported to possess diverse physiological and bioactive activities, including anticancer activity (66). Ulvan has been demonstrated to decrease viability in cancer cells while leaving healthy cells unaffected (65). The current study has categorically proven that biogenic silver nanoparticles (AgNP), which were generated *via* an extract of the marine alga *Ulva lactuca*, can induce p53-dependent apoptosis in colon cancer HCT-116 cells (31, 32).

TABLE 1 The effects of active components isolated from seaweeds on colorectal cancer.

Seaweed	Division	Therapeutic ingredients	Cell line	IC_{50}	References
Sphaerococcus coronopifolius	Rhodophyta	Dichloromethane extract	Caco-2	21.3 µg/mL	(20)
Sargassum oligocystom	Phaeophyta	Hydroalcoholic extract	CT-26	-	(21)
Porphyra haitanensis	Rhodophyta	PHP-F1, PHP-F2 and PHP-F3	HT-29	664.4 µg/mL, 575.1 µg/mL and 578.3 µg/mL	(27)
Capsosiphon fulvescens	Chlorophyta	SPS-CF	HT-29	-	(28)
Jania rubens	Rhodophyta	*J. rubens* polysaccharide	Caco-2	20 mg/mL	(29)
Red Seaweeds	Rhodophyta	AHG	HCT-116	-	(30)
Ulva lactuca	Chlorophyta	AgNP	HCT-116	142 µM	(31)
Ulva lactuca	Chlorophyta	Ulvan polysaccharide	HCT-116	22.65 µg/mL	(32)
Fucus evanescens	Phaeophyta	Laminarin	HCT-116	200 µg/mL	(33)
Kappaphycus alvarezii	Rhodophyta	κ-carrageenan	HCT-116 HT-29	- 73.87 µg/mL	(34, 35)
Fucus vesiculosus	Phaeophyta	Fucoidan	HT-29 HCT-116	200 µg/mL -	(36–38)
Fucus evanescens	Phaeophyta	Fucoidan	HCT-116	-	(39)
Sargassum mcclurei	Phaeophyta	SmF1, SmF2 and SmF3	DLD-1	-	(40)
Sargassum glaucescens	Phaeophyta	SG4	HT-29	272 µg/mL	(41)
Sargassum cinereum	Phaeophyta	Fucoidan	Caco-2	250 µg/mL	(42)
Halimeda opuntia	Chlorophyta	Carotenoids, chlorophyll a	HT-29	45.23 µg/mL	(43)
Laminaria japonica	Phaeophyta	Fucoxanthin	HCT-116	-	(44)
Sargassum angustifolium	Phaeophyta	Fucosterol	HT-29	70.41 µg/mL	(45)
Pterocladiella capillacea	Rhodophyta	Mertensene	HT-29	56.5 µg/mL	(46)
Cystoseira usneoides	Phaeophyta	Meroterpenoids	HT-29	7.8–36.9 µg/mL	(3)

IC_{50}, the half-maximal inhibitory concentration.

Laminarin

Laminarin, sometimes referred to as laminaran, which is an essential biodegradable and non-toxic polysaccharide isolated from the cell wall reservoirs of brown algae, has caught the interest of researchers (67). Laminarins are essentially a group of low-molecular-weight storage β-glucans consisting of (1,3)-β-D-glucan (68). (1,3)-β-D-glucopyranose residues with a few 6-O-branching on the main chain, and also several β-(1,6)-intra-chain links, which are abundant in their structures (69). β-glucans can promote cell apoptosis of colon cancer, and they may be beneficial natural agents for colon cancer treatment and chemoprevention (70). Additionally, certain studies have suggested that the biological activity of laminarin can be strengthened with particular chemical modifications (71). For example, Ji et al. (71) demonstrated that laminarin treated with sulfated provided a stronger antitumor effect compared with unmodified laminarin in human colorectal adenocarcinoma cells. The cell survival rate was significantly decreased after culturing with sulfated laminarin in LoVo cells. Apparently, peculiarities of the polysaccharide structure and sulfation contribute to the anticancer activity of laminarins. Malyarenko

et al. (33) found that the antiproliferative activity of laminarins from *Fucus evanescens* was comparable to that of their sulfated derivatives. The anticancer effect of laminarin isolated from *F. evanescens* was stronger than that of its sulfated derivatives in HCT-116 colon carcinoma cells. Ji et al. (72) proved that laminarin increased the intracellular reactive oxygen species (ROS) level, increased intracellular Ca^{2+}, decreased intracellular pH, and induced LoVo apoptosis through a mitochondrial pathway. A further study revealed that the expression of procaspase-8 and−3 was downregulated and the activity of caspase-8,−3,−6, and−7 was increased in human colon cancer LoVo cells through the TRAIL/DR pathway after treatment with laminarin (73). Thus, laminarin induces apoptosis in human colon cancer *via* the mitochondrial and DR pathways, indicating that laminarin is a potent anticancer agent.

Carrageenan

A set of sulfated polysaccharides generically described as carrageenan is present in red algae, which is the major ingredient of cell walls and interstitial spaces, acting as

TABLE 2 Properties of active components isolated from seaweed against colorectal cancer.

Therapeutic ingredients (Seaweed)	Cell line	Mechanism	Cell cycle arrest	References
Hydroalcoholic extract (*Sargassum oligocystom*)	CT-26	Upregulate APC and P53	+	(21)
PHP-F1, PHP-F2 and PHP-F3 (*Porphyra haitanensis*)	HT-29	Induce oxidative stress and apoptosis	G0–G1	(27)
SPS-CF (*Capsosiphon fulvescens*)	HT-29	Upregulate caspase-8,−9,−3 and cleavage of poly (ADP-ribose) polymerase (PARP), induce DNA fragmentation, disrupt MMP	G2/M	(28)
Polysaccharide (*Jania rubens*)	Caco-2	Upregulate Bax, caspase 8 and P53	+	(29)
AHG (Red Seaweeds)	HCT-116	Upregulate Bax, caspase-3,−9 and P53, downregulate Bcl-2 and Bcl-xL	+	(30)
AgNP (*Ulva lactuca*)	HCT-116	Upregulate Bax, P53 and P21, downregulate Bcl-2	+	(31)
Ulvan polysaccharide (*Ulva lactuca*)	HCT-116	Upregulate P53, downregulate Bcl-2	+	(32)
Laminarin (*Fucus evanescens*)	HCT-116	Anti-Proliferation, inhibit MMP-2 and MMP-9 activity	-	(33)
κ-carrageenan (*Kappaphycus alvarezii*)	HCT-116	Induce apoptotic cell death, nuclear fragmentation and apoptosome formation, downregulate XIAP and PARP-1	G1	(34)
Fucoidan (*Fucus vesiculosus*)	HT-29 HCT-116	Increase Bax, caspase-3, PARP-1 and P21, decrease Bcl-2, Cyclin D1 and E, CDK2 and CDK4	G1	(36, 38, 47)
Fucoidan (*Fucus evanescens*)	HCT-116	Decrease TOPK kinase activity, inhibit phosphorylation of TOPK (Thr 9)	-	(39)
SG4 (*Sargassum glaucescens*)	HT-29	Increase cytochrome c release, caspase-9,−3 and DNA fragmentation, disrupt MMP	sub-G1, S, and G2/M	(41)
Fucoidan (*Sargassum cinereum*)	Caco-2	Increase ROS, induce chromatin condensation	-	(42)
Fucoxanthin (*Undaria pinnatidfida*)	Caco-2 DLD-1 HT-29	Upregulate apoptosis, downregulat DNA fragmentation	-	(48)
Fucoxanthin (*Laminaria japonica*)	WiDr HCT-116	Upregulate cell cycle arrest and apoptosis, up-regulation of p21WAF1/Cip1, downregulat proliferation	G0/G1	(44)
Fucoxanthin (Marine algae)	HCT-116 HT29	Upregulate DNA damage	+	(49)
Fucoxanthinol (Brown algae)	DLD-1 HCT-116	Upregulate anoikis and integrin β1, downregulat PPARγ, Akt activation	G1	(50)
Astaxanthin (Marine source)	WiDr	Downregulat proliferation, inhibiting the MYC-mediated downregulation of microRNA-29a-3p and microRNA-200a	-	(51)
ω-3 PUFAs	LOVO	Anti-Proliferation, induce phosphorylation of YAP	-	(52)
EPA	HCT-116	Suppress EGFR and VEGFR activation pathways, downregulate VEGF and HIF1α	-	(53)
DHA	HCT-8 HT-29 HCT-116 SW480	Upregulate TNFα, ERdj5 and caspase-4, downregulate microRNA-21, inhibit RIP1 kinase and AMP-activated protein kinase α	-	(54, 55)
ARA	HT-29	Induce ER stress and apoptosis, inhibit SREBP-1 activity and DNA replication	G1/S	(56, 57)
LA	LOVO CT-26	Upregulate microRNA-494, cytochrome c release, caspase-9,−3 and ROS, downregulate MYCC and PGC1α	S and G2/M	(58, 59)
Fucosterol	HT-29	Anti-Proliferation, upregulate P53, decrease cell viability	+	(60)
Fucosterol (*Sargassum angustifolium*)	HT-29	Induce cytotoxicity	-	(45)
Mertensene (*Pterocladiella capillacea*)	HT-29	Upregulate caspase-3 and cleavage of poly (ADP-ribose) polymerase (PARP), inhibit phosphorylation of P53, Rb, cdc2 and chkp2	G2/M	(46)
Meroterpenoids (*Cystoseira usneoides*)	HT-29	Inhibit phosphorylation of ERK, JKN and AKT	G2/M	(3)
Phloroglucinol	HT-29 HCT-116	Upregulate caspase-3 and caspase-8, inhibited the expression of Ras, Raf, mitogen-activated protein kinase, extracellular-signal regulated kinase phosphorylation, PI3K and Akt	G0/G1	(61)

+, effects reported; −, no effects reported.

structural compounds and supplying intercellular adhesion and signaling. The structural units of these natural polysaccharides are a mixture of sulfated linear galactans, which consist of disaccharides of α-(1,4)-linked D-galactopyranose (D) residues or 3,6-anhydrogalactopyranose (DA) and β-(1,3)-linked D-galactopyranose (G) residues (74). According to the concentration, position, and sulfation of 3,6-anhydrogalactose, they are categorized into κ, λ, ι, ν, m, and θ types (75). Polysaccharides with a molecular weight ranging from 500 to 1,000 kDa are present in most of them; however, up to 25% of them may contain polysaccharides at a molecular weight of <100 kDa (76). The significant anticancer and antitumor activities were found in the low-molecular-weight κ- and λ-carrageenan, probably attributed to their antiviral and antioxidant effects as well as the stimulation of immunity against tumors (77). Some studies have reported that the risk of colon cancer appears to be minimized with low-molecular-weight carrageenan, a type of functional food ingredient (34). Carrageenans from *Gigartina pistillata* (78), *Apostichopus japonicus* (79) and *Kappaphycus alvarezii* (80) have an anti-CRC effect on the colon cancer HT-29 cell line. Native carrageenan exerted high cell suppressive activity in colon cancer cells compared with commercial carrageenan. Raman et al. (34) examined the role of the κ-carrageenan-containing soluble dietary fiber fraction of red algae in human colon cancer HCT-116 cells.

However, conflicting studies have suggested that colitis and inflammation may be induced by carrageenan (81). Wei et al. (82) suggested that the existing intestinal inflammation was magnified and TNBS-induced intestinal inflammation was aggravated by κ-carrageenan *via* activating the TLR4-NF-κB and MAPK/ERK1/2 pathways, which indicates it might act as a potential pro-inflammatory factor. In addition, further studies from their group revealed that the LPS-induced inflammation can be synergistically activated by κ-carrageenan through the Bcl10-NF-κB pathway, as illustrated by the aggravation of *Citrobacter freundii* DBS100-induced colitis in mice treated with it (83). Mi et al. (84) investigated the effectiveness of the carrageenan intake form and host intestinal microecology on toxicity in C57BL/6J mice. The severity of colitis in high-fat diet-fed mice could be increased by native carrageenan from drinking water *via* decreasing the abundance of the anti-inflammatory bacterium *Akkermansia muciniphila* and increasing that of harmful bacteria. The inflammatory effect and secretion of proinflammatory cytokines in HT-29 cells can be increased and promoted by using the fermentation supernatants of κ-carrageenan oligosaccharides (85). The inflammatory property of κ-carrageenan oligosaccharides in the context of gut microbiota was evidenced by these results.

Fucoidan

Sulfated L-fucose present in the fibrous cell walls and intercellular spaces of brown seaweeds is a major component of fucoidan, which belongs to a large family of marine sulfated polysaccharides (86, 87). Fucoidan is a heparin-like molecule with a simple chemical structure composed of a repeating unit of disaccharides containing α-1,3-linked fucose and α-1,4-linked fucose with branches linked at the C2 positions (86). Generally, L-fucose polymerized with sulfated ester groups is present substantially in fucoidan, while galactose, glucose, mannose, xylose, and glucuronic acid residues are found in only a small proportion (88). Derivatives of fucoidan with a molecular weight varying from 40 to 330 kDa have been examined for their anticancer activities (89). Numerous experiments have shown that tumor cell proliferation and its growth or metastasis can be counteracted by fucoidan *via* eliciting cell apoptosis and suppressing angiogenesis (90). Health can be promoted and gut dysbiosis can be treated by fucoidan, a potential intestinal microbiota modulator. In addition, the effects of induced apoptosis in CRC cells by fucoidan have been evaluated (91).

In HT-29 colon cancer cells, cell viability was reduced by fucoidan in a dose- and time-dependent manner through reducing the expression of CDK2, CDK4, and Cyclin D1 (36). Apoptosis was also mediated by fucoidan *via* inhibition of the IGF-I/IGF-IR/IRS-1/PI3K/AKT (92) and PI3K-Akt-mTOR signaling pathways (37). A further study found that cell cycle arrest at G1-phase was induced by fucoidan *via* the upregulation of p21WAF1 and downregulation of Cyclin D1/CDK4 and Cyclin E/CDK2 expression (47).

In HCT-116 human colon cancer cells, CDK activity was suppressed by fucoidan *via* combining the CDK inhibitor proteins p21 and p27 with the Cyclin/CDK complexes (38). EGF-induced neoplastic cell transformation was significantly inhibited by fucoidan from *F. evanescens via* suppressing the TOPK/ERK1/2/MSK 1 signaling axis (39). In colon cancer cells DLD-1, fucoidan from *Sargassum mcclurei* was observed to be less cytotoxic and inhibited colony formation (40).

Fucoidan strongly regulated the mitochondrial membrane in cancer cells. The evidence found that apoptosis was caused by fucoidan through MMP loss, an increase in cytochrome c release and DNA fragmentation, activated caspase-9 and−3, and an increasing percentage of early and late apoptotic cells in HT-29 cells. Other biological studies indicated that apoptosis was induced by SG4 *via* involvement of the Akt/mTOR/S6 pathway in HT-29 cells (41). Another report showed that fucoidan from *Sargassum cinereum* suppressed the proliferation of Caco-2 cells in a dose-dependent manner, increased ROS production, and augmented mitochondrial membrane permeability (42).

In an animal model, tumor morbidity and average tumor weight were reduced and cellular apoptosis was increased by the treatment of dietary fucoidan in 1,2-

dimethylhydrazine (DMH)-induced colorectal carcinogenesis in rats. The expression of β-catenin, C-Myc, Cyclin D1, and Survivin was reduced by treatment with fucoidan, whereas the Hippo pathway was highly activated and the phosphorylation levels of Mst1, Mst2, LATS1, LATS2, and YAP were significantly upregulated (91).

Pigments

Generally, marine seaweed and animals are rich in pigments, which are widely used in functional food and pharmaceutical industries (93). There are mainly three types of pigments in seaweed involving chlorophylls, carotenoids, and phycobiliproteins (94). The seaweed color was determined by the content and type of pigments (95). For instance, chlorophylls a and b contribute to the green color in green seaweed, whereas allophycocyanin and c-phycoerythrin are responsible for the red color in red seaweed. β-carotene and fucoxanthin (Fx) are commonly observed in brown seaweed (96).

Tumor cells from CRC patients grow uninhibited in the body and enter the blood vessels to spread systemically (97). The apoptosis mechanism is strongly associated with antioxidant properties. Hence, anticancer compounds generally have antioxidant, antiangiogenic, and anti-inflammatory effects to regulate tumor development (98). A recent report showed that the strong antioxidant activity of carotenoids and chlorophyll a from green seaweed *Halimeda opuntia* against HT-29 human colorectal adenocarcinoma was investigated. The finding suggests that natural pigments are potential anticancer ingredients (43).

Carotenoids give seaweed colors from yellow to orangish (99), which of them possess strong activities involving Fx, astaxanthin (AXT), and violaxanthin (100). The evidence showed that carotenoids inhibited the PI3K/Akt apoptosis pathway, eventually integrating the mitochondrial membrane (101).

Fx is one of the most famous lipophilic carotenoids in brown algae, which is responsible for the strong antitumor property. Clinical trials reported that Fx decreased the causing risk of CRC, which has been found to Fx possess potential anti-CRC activity *via* downregulation of tumor-related proteins (102).

In cell experiments, Fx caused a markedly decrease of the survival rate in Caco-2, HT-29, DLD-1 (48), and HCT-116 colorectal carcinoma cells (103). It was found that the activation of apoptosis and fragmentation of DNA contributes to the anticancer effect of Fx. Fx showed a significant antiproliferative effect by controlling the level of signaling proteins such as MAPK, NF-κB, and caspase family (99, 104). The disruption of cell cycle arrest causes cell apoptosis. Researchers found that Fx regulated sub-G1 cell cycle arrest in WiDr colon cancer cells (44). Furthermore, Fx stimulated cell cycle arrest at the G0/G1 or G2/M phases and caused programmed cell death

(104). It is deduced that Fx induced cell cycle arrest and caused programmed cell death through enhancing intercellular communication between tumor cells.

The derivative compound of Fx was found that exists stronger anticancer activity than Fx. Chemical structural factors significantly influence the antiproliferative properties of Fx. The anti-CRC effect of Fx-degrading compounds was evaluated in Caco-2 cells and its activity may result in partial structures (105). The 13-cis and 13′-cis isomers of Fx showed a markably cancer-preventive effect compared to other derivatives (106). In another study, the antiproliferative effects of 5-fluorouracil (5-Fu) and Fx were determined and compared in HCT-116 and HT-29 cells (49). Fucoxanthinol (FxOH) is the deacetylated type of Fx, which can induce DLD-1 cell apoptosis into anoikis-like changes through the distribution of FAK and integrin β1 expression (50). The mechanism of the anti-CRC effect of FxOH was evaluated *via* regulation of MAPK and STAT apoptosis pathways in HT-29 and HCT-116 cell lines (107), and through inhibiting NF-κB activation in CRC cells (108). According to the previous reports, we found that the anti-CRC activity of FxOH is stronger than Fx, and FxOH induced cancer cells through downregulation of MAPK, STAT, and NF-κB apoptosis pathways. The anticancer effects of Fx and FxOH on six types of CRC cell lines and twenty kinds of tissues from surgically resected clinical CRC specimens were determined as well (109).

In a CRC model animal experiment, a continuous 5-week oral administration of Fx-rich fraction strongly inhibited the number of colorectal adenocarcinomas in DSS-treated male mice (110). Additionally, Fx significantly suppressed colon cancer in azoxymethane-dextrane sodium sulfate (AOM/DSS) carcinogenic model mice (111). In an inflammation-associated CRC mouse model, after a 4-month period of Fx administration, the multiplicity of colorectal adenocarcinoma was strongly decreased *via* upregulated anoikis-like integrin β1$^{low/-}$/cleaved caspase-3^{high} cells in colonic mucosal crypts (112). Additionally, Fx also markedly decreased HSP70 protein in colorectal mucosal crypts for 15-week administration (113). In a 14-week administration in a CRC mouse model, Fx markedly decreased CCR1, pAKT(Ser473), Cyclin D1, and pSmad2 compared with untreated mice (114). Therefore, Fx had chemopreventive potency and therapy ability in the progression of colorectal carcinogenesis in mice.

AXT is mainly contained in seaweed, and showed anti-metastatic activity through inhibiting microRNA-29a-3p and microRNA-200a, thereby downregulating MMP2 and ZEB1 (51). Natural AXT isolated from *Haematococcus pluvialis* showed a significantly anti-CRC effect in a dose-dependent manner in HCT-116 cells by regulating the ratio of Bax/Bcl-2 and upregulating the phosphorylation of p38, JNK, and ERK1/2 (115). AXT induced programmed cell death in DMH-induced rat colon carcinogenesis by modifying NF-κB, COX-2, MMPs-2/9, Akt, and ERK-2 expressions (116). A finding observed that AXT inhibits the progression of colonic premalignant lesions in

an obesity-associated colorectal carcinogenesis animal model by attenuating oxidative stress, reducing inflammation and NF-κB activation in the colonic mucosa (117). Hence, AXT is a potential cancer-preventive compound in the therapy of CRC.

Polyunsaturated fatty acids

Seaweeds are known as low-energy food. Despite their low lipid content, seaweeds contain ω-3 and ω-6 polyunsaturated fatty acids (PUFAs) as a significant portion of their lipids (118). PUFAs are the precursors of eicosanoids and all cell membrane components, which can effectively reduce the risk of cancer (119). Several studies have demonstrated that the colorectal tissue distribution of PUFAs is associated with CRC prognosis (120). There are studies suggesting the potential use of some oxidized metabolites of PUFAs as biomarkers of CRC (121).

ω-3 PUFAs

PUFAs in seaweeds contain a substantial amount of ω-3 fatty acids as major components. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in seaweed are important ω-3 fatty acids in the marine environment (122). At present, more and more epidemiology and experiments have verified the antitumor activity of ω-3 PUFAs (123). Consumption of diets rich in ω-3 PUFAs not only inhibits the proliferation of CRC cells, but also can be combined with chemotherapy to enhance their sensitivity (124).

PUFAs have pro-apoptotic and growth-inhibitory effects on cancer cells. In LoVo and RKO colon cancer cells, PUFAs can reduce the synthesis of PGE2 and LTB4, inhibit the expression of ALOX5, LTB4, mPGES, COX-2, and PGE2, and increase the expression of LXA4, thereby promoting apoptosis and inhibiting the growth of LoVo and RKO colon cancer cells (125).

In an animal model, dietary supplementation of ω-3 PUFAs increased CRC cell apoptosis and decreased the tumor incidence in AOM/DSS-induced CRC in mice. ω-3 PUFAs treatment activated the hippo pathway, with increased cytoplasmic retention and phosphorylation of YAP (mediated by LATS1 and MST1/2) and the levels of epoxydocosapentaenoic acids (52). Notably, dietary ω-3 PUFAs treatment suppressed the growth of MC38 colorectal tumors. In C57BL/6 mice, ω-3 PUFAs modulate eicosanoid and fatty acid metabolite profiles (126). Huang et al. (127) demonstrated that ω-3 PUFAs reduced tumor incidence in rats by regulation of the DNA methylation process. Together, these results support the notion that ω-3 PUFAs might contribute to the anti-CRC effects of seaweed.

EPA

There is evidence of the utility of ω-3 PUFA EPA in the treatment of CRC (128). In a clinical study, patients with familial adenomatous polyposis (FAP) were randomized to receive free fatty acid (FFA). Experimental data proved that EPA 2 g daily in the form of FFA has chemo-preventive efficacy in FAP patients (129). Recently, it has been shown that EPA can prevent FAP-related CRC by acting on several molecular mechanisms (129, 130).

The increased risk of colitis-associated colorectal cancer (CAC) is strongly associated with inflammatory bowel disease, but the effectiveness of dietary EPA-FFA in anti-inflammatory and anticancer activities is unclear. In EPA-FFA-treated AOM-DSS mice, Piazzi et al. (131) found an enrichment of *Lactobacillus species* in the gut microbiota, as well as restored Notch signaling and decreased nuclear β-catenin expression, while tumor cell apoptosis increased. Morin et al. (53) reported that the eicosapentaenoic acid monoglyceride (MAG-EPA) treatment increased HCT-116 cell apoptosis and decreased the tumor of a mouse xenograft model of HCT-116 *via* activating the vascular endothelial growth factor (VEGF) receptor pathway and decreasing the epidermal growth factor receptor (EGFR).

DHA

As an ω-3 PUFA, DHA has various biological properties, including anticancer activity (132). The anticancer effect of DHA might be a consequence of its ability to regulate the production of proinflammatory mediators in cancer cells and/or host cells, changing the inflammatory status of the systemic or tumor microenvironment (54, 133). Numerous studies have demonstrated that in CRC cells, the activity of DHA-triggered caspase family members is associated with apoptosis (134). Mechanisms including DHA-induced cellular protein expression explain the antitumor activity of DHA (55).

Fluckiger et al. (54) reported that the TNFα-dependent manner triggers apoptosis in HCT-116, HCT-8, and human CRC cells in DHA-mediated, and cells induced with DHA increased TNFα mRNA content by downregulating microRNA-21 expression, stating that the effect of TNFα on DHA-mediated apoptosis of colon cancer cells. Sarabi et al. (135) demonstrated that DHA could specifically attenuate promoter DNA methylation and VEGF protein levels of microRNA-126 in HCT-116, Caco-2, and CRC cells. Fasano et al. (55) reported that DHA treatment induced apoptosis in HT-29, HCT-116, and SW480 colon cancer cell lines and inhibited their total and surface GRP78 expression, suggesting that pERK1/2 could be the first upstream target of DHA. These studies offer insight into the epigenetic mechanisms by which DHA influences gene expression regulation in CRC cells.

ω-6 PUFAs

The ω-6 PUFAs contained in seaweeds include mostly linoleic acid (LA) and arachidonic acid (ARA) (136). Previous studies have suggested that, unlike ω-3 PUFAs, the ω-6 PUFAs, especially ARA, are generally associated with many adverse effects on the human body, including the promotion of multiple

cancer types, such as CRC (137, 138). However, there is little *in vitro* evidence to show that ARA exerts anticancer activity in CRC cells. Bae et al. (56) and González-Fernández et al. (57) evidenced that ARA may inhibit DNA replication and G1/S cell cycle transition and induce endoplasmic reticulum stress in HT-29 CRC cells, thereby suppressing cell viability and inducing apoptosis.

Research evidence shows that LA may be involved in both pro- and anticancer activities (137). Lu et al. (139) and Ohmori et al. (140) reported that LA at low concentrations (100-200 μM) reduced caspase-3 activation in CRC cells and promoted tumor cell proliferation. LA at high concentrations (above 300μM) enhanced ROS generation, caused mitochondrial dysfunction and inhibited tumor cell growth (58). A recent report from Ogata et al. (59) suggested that LA induced quiescence by promoting microRNA-494 expression, resulting in the dormancy of CT-26 CRC cells. Therefore, it is speculated that LA can inhibit the growth of CRC cells.

Phytosterols

Phytosterols are the major nutritional components of seaweed and the most important chemical constituents of algae (141). Phytosterols are the major lipid components of plant cell biofilms. In the marine environment, brown algae are a major source of phytosterols, including brassicosterols with a small amount of plant cholesterol and fucosanols (142). Not only can phytosterols lower cholesterol, they also have strong anticancer activity, and several studies have shown that foods rich in phytosterols may help control the growth of many types of tumors (143).

β-Sitosterol

β-Sitosterol, isolated from seaweed, is the most common dietary phytosterol and has a proven potential role in the treatment of CRC (144, 145). Shathviha et al. (146) reported on the evaluation of AgNP synthesized using β-sitosterol and its cytotoxic potential in HT-29 human colon cancer cells. β-Sitosterol-mediated AgNP treatments induced p53 expression and early apoptosis in HT-29 cells. Arul et al. (147) investigated the β-Sitosterol significantly reduces fecal bacteria and colonic bioconverting enzymes in mice with DMH-induced colon cancer, thereby preventing colon cancer development. Amplified activities of colonic biotransformation enzymes are considered hallmarks of colon carcinogenesis. Hence, β-sitosterol is a potential chemopreventive agent in colon carcinogenesis.

Fucosterol

The major phytosterol in brown seaweed is fucosterol, which has various biological activities, including anticancer activity (148). A previous study indicated that oxygenated fucosterol inhibited HCT-116 human colon cancer cell growth with higher cytotoxicity than commercial cytotoxic drugs (149). Ramos et al. (60) reported that the combination of fucosterol with 5-Fu can enhance the toxic effect in HT-29 cells. Furthermore, fucosterol is not toxic to normal cells, indicating specificity for cancer cells. The hexane fraction of fucosterol produced by *Sargassum angustifolium* confirmed its cytotoxic activity against HT-29 (45).

Terpenes

Within the marine environment, terpenes synthesized by algae and secreted to the outside of cells to resist environmental insults are major secondary metabolites from seaweeds (150). It is a chemical compound that contains one or more isoprene units with strong anticancer activity (15). Epidemiological and experimental studies suggest that terpenes may be helpful in curbing the growth of a variety of cancer cells, including colon cells, and provide additional opportunities for cancer therapy (151). Terpenes can modulate pathophysiological processes such as the cell cycle, invasion, migration, proliferation, and apoptosis in different types of tumor cells (152), exhibiting a wide spectrum of antitumor activities (153).

Previous studies have reported that a pentahalogenated monoterpene, halomon, isolated from the red seaweed *Portieria hornemannii*, exhibited strong anticancer activity (154). The halogenated monoterpene mertensene from the red seaweed *Pterocladiella capillacea* (S.G. Gmelin) Santelices & Hommersand inhibited LS174 and HT-29 human colorectal adenocarcinoma cell lines by activating caspase-3 and NF-κB, Akt, and MAPK ERK-1/-2 pathways vitality (46). Terpenes from the brown seaweed *Cystoseira usneoides* have anticancer effects on HT-29 colon cancer cells by reducing the phosphorylation levels of JNK and ERK and inhibiting the ERK/JNK/AKT signaling pathway (3). These reports demonstrate the potential of terpenes as drug candidates for the treatment of colon cancer.

Phenolics

Phenolic agents are one of the most active compounds in seaweed. Polyphenols with their high molecular weight, such as phlorotannins, specifically exist in brown algae (155). Phlorotannins are composed of a number of phloroglucinol (Ph) monomeric units (156). Those active compounds play a pivotal role in anti-CRC effects, for instance, as apoptotic, anti-metastatic, and antiangiogenic proprieties. They inhibited CRC cell growth directly or indirectly through attenuated inflammatory cytokines and oxidative stress (157). In other reports, the anticancer effects of Ph on insulin-like growth factor-1 receptor signaling in HT-29 human colon cancer cells

have been investigated. In addition, Ph inhibited the levels of Ras, mitogen-activated protein kinase, and mTOR (158). The polyphenol-rich agent showed a lower survival rate in CRC cells than the non-polyphenol-rich agent from seaweeds involving *Laminaria japonica*, *U. lactuca*, and *Porphyra tenera*. Additionally, the polyphenol-rich agent caused G0/G1 cell cycle arrest in HCT-116 cells (159). Phlorofucofuroeckol A (PFF-A) (160) and Ph (161), isolated from brown seaweed, decreased survival rates via activating the apoptosis pathway in CRC cells. Further, Ph decreased the survival rate dose-dependently and induced apoptosis in HT-29 cells, altering Bcl-2 and caspase family proteins (61). The evidence proved that phenolic agents play an important role in understanding the development of colon CRC.

Vitamins

Seaweed is an important source of various vitamins, among which vitamin C and vitamin D have strong anticancer activity (162). A previous study indicated a potential interplay of vitamin D and immune cells in the tumor microenvironment reduces CRC risk (163). Moreover, some research groups have reported an inverse association between vitamin D3 levels and CRC incidence, and that higher vitamin D3 levels reduce polyp recurrence and improve overall survival in CRC patients (164, 165). Tumor migration and proliferation were inhibited by vitamin D and its analogs in the colon of C57Bl/6 mice (166). Rawson et al. (167) suggested that vitamin D may alter CRC risk by mediating extracellular inhibition. Ferrer-Mayorga et al. (168) indicated that the vitamin D metabolite calcitriol promotes vitamin D receptor expression and inhibits fibroblasts (associated with colon cancer), resulting in anti-CRC effects. There is also a study on vitamin C from Yun et al. (169), who found that cultured CRC cells harboring KRAS or BRAF mutations were selectively killed when exposed to high levels of vitamin C.

Minerals

The minerals in seaweed are 10–20 times those of land plants and are easily bio-accumulated from seawater (12, 170). The macronutrients (e.g., magnesium, potassium, calcium, and sodium) and microelements (e.g., selenium, iodine, iron, manganese, and zinc) contained in seaweed are important for normal physiological functioning of the body and have potential relevance in cancer treatment (171, 172). Numerous clinical and epidemiological studies indicated that the risk of CRC may be reduced with a higher intake of calcium and magnesium (173). Ali et al. (174) evaluated the antitumor effect of selenium against DMH-induced CRC in BALB/C mice and its effect on apoptosis and angiogenesis. The group

treated with DMH plus selenium exhibited significantly lower expression of cloned caudal-type homeobox gene-2 and VEGF but a higher caspase-3 expression level than the DMH-treated group.

Conclusions

Many studies have demonstrated the effect and mechanism of red, green, and brown seaweeds in CRC-prevention and therapy. Various therapeutic compounds from seaweed involving large molecular polysaccharides and small molecular pigments, fatty acids, phytosterols, terpenes, phenolics, vitamins and minerals induce programmed cell death *via* various signaling pathways. Such treatments can alter the protein expression of Bax, caspases, Bcl-2, MAPK, NF-κB, VEGF, DNA methylation, and CDK inhibitor and induce changes in the cell cycle and the CRC cellular functions of adhesion, migration, and invasion. Important anti-CRC agents such as polysaccharides and fatty acids existed for their antiproliferative and anti-metastatic effects *in vivo*. Furthermore, terpenes and pigments inhibited CRC cell survival rate and induced programmed cell death *via* regulation of the Akt signaling pathway.

A few molecular alterations in human CRC cells were correspondingly observed in CRC animal models treated with seaweed. Consecutive studies *in vitro* will be important as the basis for clarifying the molecular mechanisms underlying cancer prevention in humans with CRC and CRC animal models. CRC animal models, AOM-DSS, BALB/C, and C57BL/6 mice, have been the vehicles for many discoveries concerning the anti-CRC effects of seaweed. The oxidation, inflammation and gut microbiota, which are significant factors associated with colorectal carcinogenesis, have been reported to be prime targets of various therapeutic compounds from seaweed. In addition, the administration of Fx induced anoikis in CRC animal models. However, the detailed molecular mechanisms underlying the cancer chemopreventive effect in animals remain poorly understood.

Finally, this review highlights the importance of seaweed as a potential agent candidate for preventing CRC. However, the underlying mechanisms remain elusive. Further clinical investigations are needed to assess the anticancer effect of seaweed in humans.

Author contributions

YD and ZP conceptualized the idea and scope of the review. YZ, XZ, HY, and KZ both performed a literature review. YF and DX wrote the manuscript and created the figures. All authors critically revised and edited the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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