CHAPTER 16

Anticancer Compounds from Marine Macroalgae and Their Application as Medicinal Foods

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Contents

Abstract

Cancer is one of the most challenging medical conditions that need a proper therapeutic approach for its proper management with fewer side effects. Until now, many of the phytochemicals from terrestrial origin have been assessed for their anticancer ability and few of them are in clinical trials too. However, marine environment also has been a greatest resource that harbors taxonomically diverse and a variety of life forms and serves as store house for several biologically beneficial metabolites. Hitherto, many metabolites have been isolated from marine biomasses that have exhibited excellent biological activities, especially as anticancer agents. In particular, marine macroalgae which are considered as dietary

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constituents in Pacific Asian region have become chief resources for their unparalleled and unique metabolites like sulfated polysaccharides (SPs), phlorotannins, and their ability in reducing the risk of cancer and its related diseases. In this chapter, we have discussed the anticancer activities of marine algae-derived SPs, phlorotannins, and carotenoids and the possibilities of marine algae as potential medicinal foods in the management of cancer.

I. INTRODUCTION

Cancer is a dreadful pathological condition that remains one of the high-ranking causes of death in the world though there are considerable therapeutic approaches for its management. It is considered as the second life-taking disease which is preceded by heart diseases. Moreover, it is estimated that by 2020 cancer would be accounting for more than 10.3 million deaths per year if more secure and effective therapeutic approaches are not devised to cure cancer (Schumacher *et al*., 2011). Though there is an appreciable advancement in chemotherapy and therapeutic medicines for the management of cancer, the search for novel and safe anticancer treatments continues. Due to the shortcomings like high toxicity and unwanted side effects by the synthetic drugs, the natural products derived from medicinal plants have gained significance in the treatment of cancer. The National Cancer Institute (NCI) of the USA has screened about 1,14,000 extracts from an estimated 35,000 plant samples against a number of tumor systems. Of the 92 anticancer drugs commercially available prior to 1983 in the USA and approved worldwide between 1983 and 1994, approximately 62% can be related to natural origin (Cragg *et al*., 1997). According to the WHO, 80% of the world's population, primarily those of developing countries, rely on plant-derived medicines for the health care. Natural products and their derivatives represent more than 50% of all the drugs in clinical use of the world. Higher plants contribute not less than 25% of the total. Almost 60% of drugs approved for cancer treatment are of natural origin. Fruits and vegetables are the principal sources of vitamins C, B, E, carotenoids, and fibers, and these contribute to the apparent cancer-protective effects of the foods. Moreover, the increased dietary intake of natural antioxidants can reduce the risk of lifestyle diseases like heart diseases, and cancer mortality, and helps for a longer life expectancy (Gurib-Fakim, 2006; Halliwell, 2007; Rios *et al*., 2009).

For many years, research has essentially focused on plants and terrestrial microorganisms, mainly because these specimens are easily available and folk traditions have described beneficial effects from their use. Recently, there is an increase in the screening of potential drug candidates

from plant origin which include anticancer compounds like vinblastine and vincristine (*Catharanthus roseus*), epipodophyllotoxin, an isomer of podophyllotoxin (*Podophyllum peltatum* roots), paclitaxel (*Taxus baccata*, *Taxus brevifolia*, *Taxus canadensis*), camptothecin (*Camptotheca acuminata*), homoharringtonine (*Cephalotaxus harringtonia* var. *drupacea*), elliptinium (*Bleekeria vitensis*), flavopiridol (*Dysoxylum binectariferum*), and ipomeanol (*Ipomoea batatas*). However, based on the fact of the lack of natural defense systems, the metabolites produced by the marine organisms to evade potential threats have gained much preference in the field of science for potential medicinal compounds. It is well understood that these metabolites help the marine organisms to sustain and cope up with the harsh and vulnerable conditions that marine environment offers them. As a matter of fact, this silent world, in other words, marine environment, is many folds richer in its biodiversity that makes marine organisms and their metabolites unique. Efforts to exploit this biodiversity through the identification of new chemical compounds have only begun: approximately 22,000 natural products of marine origin have been discovered so far, whereas 131,000 terrestrial natural products exist (Blunt *et al*., 2011).

Based on the above facts, in recent times, the isolation and characterization of the biologically active components from marine algae have gained attention from various research groups across the world. Among marine algae, brown algal species such as *Ecklonia cava*, *Eisenia arborea*, *Ecklonia stolinifera*, and *Eisenia bicyclis* have been studied for their potential biological activities. Majority of the investigations on the metabolites derived from brown algae have revealed their potentiality as antioxidant, anti-inflammatory, antidiabetic, antitumor, antihypertensive, and antiallergic, and in hyaluronidase enzyme inhibition and matrix metalloproteinases (MMPs) inhibition. The marine algae have been studied for biologically active components that include sulfated polysaccharides (SPs), phlorotannins, carotenoids, sterols, etc. In this chapter, we have made an attempt to throw light on the potential anticancer activities of marine algal metabolites.

II. POTENTIAL ANTICANCER AGENTS FROM MARINE MACROALGAE

A. Sulfated polysaccharides

In the field of pharmacology, the biologically active polysaccharides (PSs) that are derived from natural sources have attained a special place for the development of drug lead molecules. Marine macroalgae contain a significant amount of soluble PSs and have potential function as dietary fiber. Specially, brown marine algae are known to produce functional PSs such as alginates and fucoidans. Seaweed-derived PSs have been

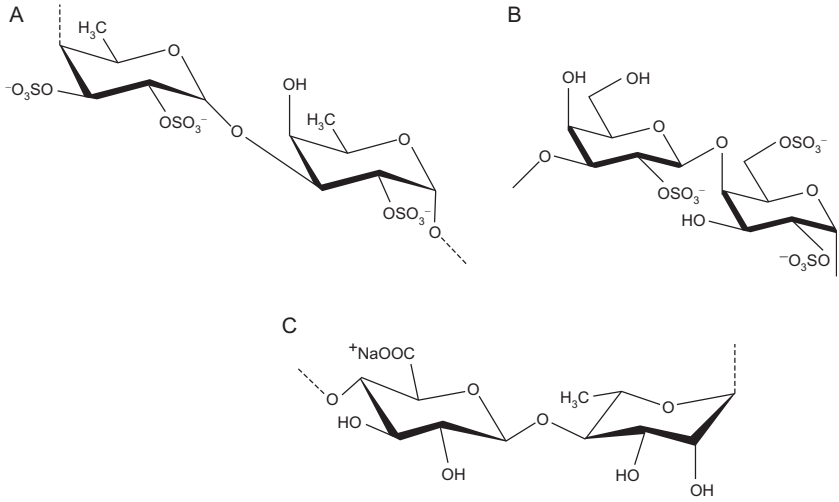

FIGURE 16.1 Monomeric units of marine-algae derived SPs (A) fucoidan, (B) carrageenan, and (C) ulvan.

reported to exhibit biological activities like anticoagulant, anti-inflammatory, antiviral, and antitumoral activities (Costa *et al.*, 2010). Among the various PSs found in seaweeds, fucoidans, carragenan, and ulvan (Fig. 16.1) have been studied for their potential role in controlling cancer.

1. Fucoidans

Fucoidan, an ingredient of marine algae, is composed of a polymer of $\alpha 1 \rightarrow 3$-linked L-fucose, with sulfate groups on some of the fucose residues at four positions (Patankar *et al.*, 1993). Out of the many biologically effective activities of fucoidans, *in vitro* and *in vivo* studies have reported that marine algae fucoidans possess antitumor, anticancer, antimetastatic, and fibrinolytic properties in mice (Religa *et al.*, 2000). In one of the *in vitro* studies, fucoidan isolated from *Laminaria guryanovae* has effectively inhibited the neoplastic cell transformation by inhibiting the phosphorylation of epidermal growth factor receptor (EGFR) in mouse epidermal JB6 Cl41 cells (Lee *et al.*, 2008). As it is evident that EGFR, one of the receptor tyrosine kinases, plays a pivotal role in regulating cell proliferation, differentiation, and transformation and is also considered as a target for the treatment of cancers, the inhibitory activity of fucoidan suggests that marine edible algae could possibly reduce the risk of cancers when considered as dietary supplements. In Asian countries such as China, Japan, and Korea, seaweeds are considered as dietary supplements and also are reported to have been used for boosting up the immune system. Mekabu (sporophyll of *Undaria pinnatifida*), a dietary alga, is reported to

exert antitumor activity and enhance the immune response. *In vivo* studies of effect of fucoidans isolated from Mekabu are reported to reduce the tumor growth. The experimental mice (T cell receptor transgenic (DO11.10—Tg)) were fed with a diet containing 1% Mekabu fucoidan, and it was reported that mice that were fed with the Mekabu fucoidan had a reduction on tumors by 65.4%. This *in vivo* study also reports that Mekabu fucoidan mediates tumor destruction through T-helper (Th1) cell and natural killer (NK) cell responses (Maruyama *et al.*, 2006). These findings clearly suggest the efficacy of marine algal fucoidans for the possible application in the treatment of tumors and cancers.

The antitumor and antimetastatic activities of fucoidan from *Fucus evanescens* have been studied *in vivo* in C57Bl/6 mice with transplanted Lewis lung adenocarcinoma. It was observed that single and repeated administration of fucoidan in dose of 10 mg/kg has exhibited moderate antitumor and antimetastatic effects and potentiated the antimetastatic, but not antitumor, activities of cyclophosphamide (Li *et al.*, 2008).

2. Carrageenans

The linear form of SPs and carrageenans extracted from red algae has been reported to have many applications in the food industry as well as in the medicinal industry. Carrageenans, a family of SPs isolated from marine red algae, are widely used as food additives, such as emulsifiers, stabilizers, or thickeners (Campo *et al.*, 2009). Out of the various forms of carrageenans from red algae, λ-carrageenan is a sulfated galactan isolated from some red algae and has been reported to have many kinds of biological activities. One of the research groups has isolated λ-carrageenan with different molecular weights 650, 240, 140, 15, and 9.3 kDa from a Chinese red algae *Chondrus ocellatus* to study their tumor-inhibiting activities. Their research investigation on λ-carrageenan-treated mice of transplanted S180 and H22 tumor has shown considerable antitumor and immunomodulation activities in different degrees. It is although reported that molecular weight of this PS has notable antitumor and immunomodulation activities by means of activating the immunocompetence of the body (Zhou *et al.*, 2004). The antioxidant and antitumor activities of marine algal extracts are becoming popular in current days' research. Hot-water-soluble PS of the marine alga *Capsosiphon fulvescens* have been reported to exhibit inhibition activities on cultured human cancer cells in a dose-dependent manner *in vitro*. The detailed mechanistic studies at molecular level have revealed that the cancer inhibitory effect of these hot-water-soluble PSs was in correlation with an increase in caspase-3 activation and a decrease in Bcl-2 expression, thus inducing apoptosis by inhibiting IGF-IR signaling and the PI3K/Akt pathway (Kwon and Nam, 2007). The carrageenan's low cytotoxic effects and their immunomodulation and antitumor activities should be considered and can be

recommended for the anticancer therapies that can give a breakthrough for the proper management of cancer-related therapies.

3. Ulvans

Ulvans are structural acid PSs present in cell wall of green algae (*Ulva* and *Enteromorpha*). They are highly sulfated and essentially composed of rhamnose 3-sulfate, xylose, xylose 2-sulfate, glucuronic acid, and iduronic acid units. Ulvan displays several physiochemical and biological features of potential interest for food, pharmaceutical, agricultural, and chemical applications (Lahaye and Robic, 2007). Formation of free radicals due to the oxidative stress is thought to be a major contributor for the formation of cancer cells in the human body. Several research groups have suggested that low molecular weight SPs have shown potent antioxidant activity than high molecular weight SPs. For instance, different molecular weight ulvans from *Ulva pertusua* (Chlorophyceae) were investigated for H_2O_2 degradation and their antioxidant activities. Their results showed that low molecular weight ulvans have a strong antioxidant activity. The rationale for this is low molecular weight SPs may incorporate into the cells more efficiently and donate proton effectively compared to high molecular weight SPs (Qi *et al.*, 2005). This antioxidation ability of the ulvans can be exploited for the preparation of medicinal compounds that can control the progress of cancer. On the other hand, *in vitro* and *in vivo* antitumor properties of an SP isolated from the marine algae *Champia feldmannii* (Cf-PLS) have revealed that inhibition rates of sarcoma 180 tumor development were 48.62% and 48.16% at the doses of 10 and 25 mg/kg, respectively, which clearly suggest the efficacy of marine algal PSs as potential antitumor agents (Lins *et al.*, 2009). Importantly, SPs from marine algae are known to be important free-radical scavengers and antioxidants for the prevention of oxidative damage, which is an important contributor in carcinogenesis. Therefore, it might be suggested that these seaweed-derived SPs have potent capacities for new anticancer product developments in the pharmaceutical as well as in the food industries as novel chemo-preventing agents for cancer therapy (Wijesekara *et al.*, 2011). Moreover, the marine macroalgae are considered as dietary constituents and are rich in SPs like fucoidans, carrageenan, and ulvan and thus can be recommended as medicinal foods to reduce the incidence of cancers.

III. PHLOROTANNINS

It is an undeniable fact that sea algae possess enormous biologically important and beneficial ingredients that aid for the betterment of human health. Recently, the marine algal species have been widely investigated for their bioactive compounds like PSs, pyropheophytin,

tripeptides, and phlorotannins in particularly *E. cava* and *E. bicyclis* (Kousaka *et al.*, 2003). Especially, polyglucinol derivatives called phlorotannins from marine macroalgae (confined to brown algae) have gained a lot of importance in the fields of food, medicinal, and cosmeceutical industries. These phlorotannins are suggested to be formed by the polymerization of phloroglucinol (1,3,5-tryhydroxybenzene) monomer units and biosynthesized through the acetate–malonate pathway, also known as polyketide pathway. The phlorotannins are highly hydrophilic components with a wide range of molecular sizes ranging between 126 and 650 kDa. Phlorotannins are tannin derivatives composed of several phloroglucinol units linked to each other in different ways and mostly isolated from brown algae (Ragan and Glombitza, 1986; Singh and Bharate, 2006). Dioxinodehydroeckol (Fig. 16.2) isolated from *E. cava* has exhibited a remarkable antiproliferative effect on human breast cancer cells (MCF-7). Scientific investigation suggests that dioxinodehydroeckol's potential antiproliferative activity might be associated with the induction of apoptosis through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) family and NF-κB-dependent pathway (Kong *et al.*, 2009).

Phlorotannin extract (PE) derived from brown algae *Laminaria japonica* Aresch (*L. japonica*) has shown considerable antiproliferative activity in the human hepatocellular carcinoma cell line (BEL-7402) and on murine leukemic cell line (P388) in a dose-dependent manner. Microscopic observation have revealed that the morphologic features of tumor cells treated with PE and 5-fluorouracil (a commercial chemotherapy drug) are markedly different from the normal control group, suggesting the antiproliferative effect of PE (Yang *et al.*, 2010). In pretumor bearing mouse, the dietary feeding (0.1% and 0.5%) of brown algae polyphenols significantly reduced tumor multiplicity (45% and 56%) and tumor volume (54% and 65%), and topical administration (3 and 6 mg) significantly decreased tumor multiplicity (60% and 46%) and tumor volume (66% and 57%), respectively. It is believed that brown algal polyphenols inhibit the

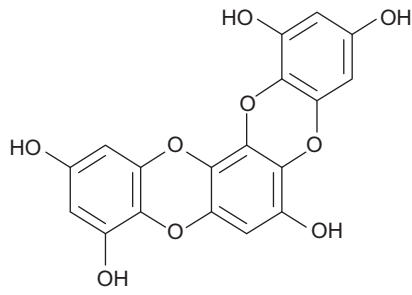

FIGURE 16.2 Dioxynodehydroeckol from *E. cava* which exhibits anticancer properties.

cyclooxygenase-2 activity and cell proliferation, hence preventing the tumor progression (Hwang *et al.*, 2006). It has been reported that the total polyphenolic content in the algae is the key for their antiproliferative ability. These scientific reports clearly suggest the importance and the ability of phlorotannins in reducing the risk of cancer and its related diseases. Thus recommending marine algae as ideal resources for novel and effective anticancer compunds and their predominant role as medicinal foods.

IV. CAROTENOIDS

Carotenoids are organic pigments that have tetraterpinoid structures and are commonly found in the photosynthetic organisms that include macroalgae. It is believed that consumption of vegetables that are rich in carotenoids and other active components could reduce the risk of malignancies in human colon, lung, and breast cancers (Block *et al.*, 1992; Le Marchand *et al.*, 1993; Zhang *et al.*, 1999). Among the carotenoids, fucoxanthin and astaxanthin (AX) (Fig. 16.3) have been known for their antioxidation activities that might help to control the progress of cancers. Fucoxanthin, a major carotenoid in brown sea algae, has recently been demonstrated by us to inhibit the proliferation of colon cancer cells, and this effect was associated with growth arrest. The molecular mechanisms of fucoxanthin against the hepatic cancer using the human hepatocarcinoma HepG2 cell line (HepG2) were evaluated. This investigation has led to confirm that fucoxanthin reduced the viability of HepG2 cells accompanied with the induction of

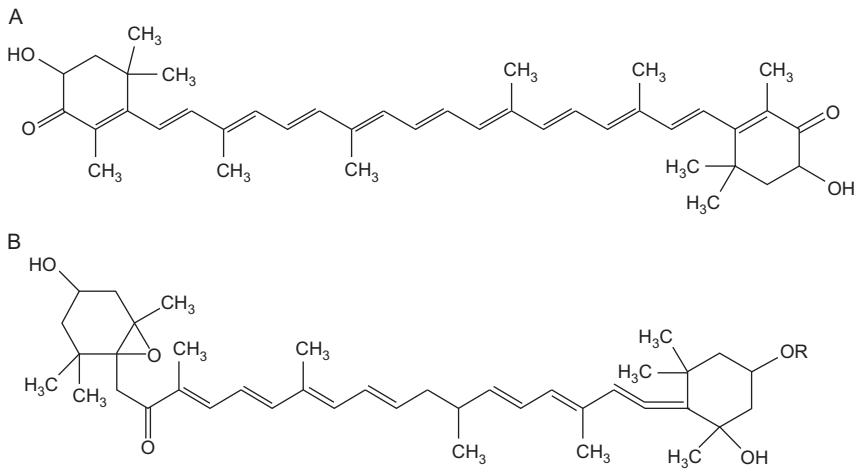

FIGURE 16.3 Marine-derived carotenoids, (A) astaxanthin and (B) fucoxanthin.

cell cycle arrest during the G_0/G_1 phase at 25 μM (Das *et al.*, 2008). The apoptosis-inducing effects of fucoxanthin from brown alga *U. pinnatifida* have been studied *in vitro* on human leukemic HL-60 cells. On treatment of HL-60 cells with fucoidan, the DNA content that was fragmented which is thought to be an enrichment factor has increased with the increase in the concentration of fucoxanthin, thus suggesting the apoptosis-inducing ability of fucoxanthin in HL-60 cells (Hosokawa *et al.*, 1999).

AX, a member of carotenoid which is found abundantly in seaweeds, also has been reported to exhibit several biological activities. The chemopreventive effects of two xanthophylls, AX and canthaxanthin (CX), on urinary bladder carcinogenesis induced by *N*-butyl-*N*(4-hydroxybutyl) nitrosamine (OH-BBN) was investigated in male ICR mice. In this investigation, it was understood that, in particular, AX administration after OH-BBN exposure significantly reduced the incidence of bladder cancer (transitional cell carcinoma) ($P > 0.003$). Moreover, preneoplasms and neoplasms induced by OH-BBN, and the antiproliferative potential, were greater for AX than CX. These results indicate that AX is a possible chemopreventive agent for bladder carcinogenesis and such an effect of AX may be partly due to suppression of cell proliferation (Tanaka *et al.*, 1994). Stress may play an important role in the incidence of several types of cancer. Studies have indicated that psychological stress enhances the initiation and progression of cancer in humans and animals (Bergsma, 1994). The inhibition of the NK cells plays a major role in the antitumor effector activity and the inhibition of cancer metastases. One of the research groups has evaluated the effect of fucoidan in stress-induced mice with inhibited NK cells. The stress also caused a significant increase in the lipid peroxidation of liver tissue. ASX (100 mg/kg/day, p.o., 4 days) improved the immunological dysfunction induced by restraint stress. Daily oral administration of ASX (1 mg/kg/day, p.o., 14 days) markedly attenuated the promotion of hepatic metastasis induced by restraint stress. These results suggested that AX improves antitumor immune responses by inhibiting lipid peroxidation induced by stress (Kurihara *et al.*, 2002). Considering these above specified research observations, marine algae that are dietary constituents could be recommended as medicinal foods because of the abundant occurrence of the secondary metabolites that act as immunomodulators for combating cancer-related diseases.

V. CONCLUSIONS AND FURTHER PROSPECTS

Marine organisms have been serving the mankind with outstanding metabolites that have remarkable and effective activities that aid for the betterment of the human health. Marine environment offers highly challenging circumstances that enable the marine organisms to synthesize

unique and effective metabolites to thrive in such harsh situations. Hence, marine organisms and their metabolites are considered as exceptional resources in the fields of food, medicinal, and pharmaceutical prospects. Moreover, since ages marine organisms like fish, algae crustaceans have been serving the human kind as food resources. Scientific investigations have already proven the effectiveness of the marine algae as functional foods that could cure various kinds of human diseases. The antioxidant and, in particular, the anticancer abilities of the sea algae derived SPs, phloroglucinol derivatives, and carotenoids have already made clear about their possible candidature as leads for the designing of anticancer medicines. Dietary intake of these algae could definitely offer humans an outstanding immunomodulation that could enhance the chances to inhibit cancers and related diseases, and hence marine macroalgae could be recommended as medicinal foods. These phytochemicals possibly activate macrophages, induce apoptosis, and prevent oxidative damage of DNA, thereby controlling carcinogenesis. However, in spite of vast resources enriched with chemicals, the marine floras are largely unexplored for anticancer lead compounds and research strategy should be focused on screening of more sea algae as potential resources for the phytochemicals that could cure this deadliest disease, human cancer. And with the available sophisticated approaches, the research should proceed for the clinical trials to establish these marine algal metabolites as potential anticancer compounds.

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