



Bioactive Compounds of Seaweeds and Their Effects on Certain Types of Cancer

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Abstract

Cancer is considered as one of the major health problems worldwide. So far, no completely effective method has been found for cancer treatment. Therefore, the rise of using natural products has been proposed as an alternative therapy in this regard. For many years, the seaweed has been a source of many functional bioactive compounds including polysaccharides, polyphenols, pigments, terpenes, and many others. These compounds have shown many bioactivities including anticancer activity against different kinds of cancer. Bioactive compounds obtained from the seaweed have been demonstrated to cause apoptosis in cancer cells and trigger cell cycle arrest with low cytotoxicity against normal cells. In this review, it was attempted to shed light on the anticancer activity of some seaweed-derived bioactive compounds.

Keywords: Cancer, Treatment, Multidrug resistance, Bioactive materials, Seaweeds, Antitumor

Background

Cancer, which is the world's second-largest cause of mortality, is the unregulated proliferation of cells and is related to significant pathological changes (1). Approximately 1.8 million people were diagnosed with cancer in the United States in 2020 (2). Further, about 140 690 cancer cases were detected and about 103 250 deaths of cancer were among the elderly in the United States (2). In addition to other types of cancer that can be metastasized into other tissues, more than 200 different types of malignant tumors are identified resulting in lethal metastasis tumors. Lung cancer was the most common and caused death among males, followed by prostate and colorectal cancer, as well as liver and stomach cancer. Among females, breast cancer, accompanied by colorectal and cervical and lung cancer, was the widely diagnosed cancer and caused deaths (3). Owing to this high degree of cancer effect, the removal of cancer has been given considerable attention (4).

However, various developed anticancer drugs can prolong the survival time of patients. The intrinsic side effects of these drugs seriously affect the quality of the patient's life (5).

Carcinogenesis Process and Certain Types of Cancer

Carcinogenesis is a multi-stage complex process controlled by processes such as inflammation, growth and cell differentiation, and metastasis (6). It has been described as

a three-stage process including initiation, promotion, and progression (7).

Cancers are categorized relative to the type of tissue and the cell they originate from (8). Carcinomas are epithelial cell-derived cancers and the most common human cancer. Sarcomas originate from muscle cells or the connective tissue. Different types of leukemia and lymphomas coming from white blood cells and their precursor cells are cancers that do not fall into any of these two large categories.

Breast cancer is one of the leading public health challenges worldwide. It is the most prevalent among women and is the world's second type of cancer with 2 088 849 new cases in 2018 (3,9). Patients with breast cancer live extremely longer as early warning programs develop and improvements in the treatment of breast cancer contribute to ever-better survival results. The survival rate for five years increased from 75% in 1976 to 91% in 2017 (10).

Liver cancer is the world's sixth most frequent form of cancer and occupies the second position in mortality after lung cancer (11). According to (12), two million people are annually died due to liver diseases, half of which are because of cirrhosis complications, and the other half is due to viral hepatitis and hepatocellular carcinoma (HCC). HCC is the main type of liver pathology and accounts for about 80% of cases of liver cancer (13). Despite continuing developments in chronic liver disease management, tumor identification, and oncological diagnosis, HCC prognosis remains lower compared to other tumor entities (3). HCC carcinogenesis

includes angiogenesis, chronic inflammation, and macro- and micro-environmental tumors (13). Regrettably, a large number of patients lose the chance for resection due to delayed diagnosis (14).

Approximately 13 430 new cases of larynx cancer have been detected, with around 3620 patients who are dying from the disease (15). Laryngeal cancer occurs more frequently in males than in females (16). This type of cancer is regrettably one of the oncology conditions for which the lifetime risk has decreased from 66% to 63% over the past 40 years whereas the overall prevalence is decreasing (10).

The pathogenesis of laryngeal cancer includes a variety of risk factors (17). Tobacco and alcohol intake is the most important of these factors. The use of tobacco is strongly associated with the incidence of laryngeal cancer, with a 10-15 significantly greater threat for smokers compared to non-smokers and a risk 30 times higher for voracious smokers (18,19).

Treatment of Cancer

Invasive cancer care is primarily dictated by the histology of the tumor, the stage of cancer, patient preference, and success status (2). The primary treatment modalities are surgery, chemotherapy, and radiation therapy (20). For the majority of solid tumors, surgery remains the best therapy. Surgery could be possible in only a small subset of patients depending on the type of cancer (21). Some modalities including chemotherapy and radiation therapy are probably paired with surgery. However, major side effects such as fatigue, diarrhea, xerostomia, and secondary malignancies may be associated with these therapies (22). Radiation therapy is the use of ionizing radiation for directly treating the cancerous tumor rather than the whole body. Chemotherapy is used to cure the whole body and applies to chemical treatment which quickly destroys all dividing cells (23).

Depending on the method of procedure, two types of procedures are commonly used in combination with each other, including neoadjuvant (pre-surgery), adjuvant (post-surgery), and concomitant treatment where radiotherapy and chemotherapy are employed with each other without operation (24). The integration of chemotherapy and radiation treatment helps many approaches to attack tumors and thus can help avoid the immunity of cancer cells to either therapy (25,26). The general course of therapy during neoadjuvant therapy includes radiation treatment accompanied by chemotherapy. It could be used to minimize tumor dimension. It has been shown that this method of treatment increases the survival rate of many cancer patients (24).

Adjuvant therapy is often used after surgery as there is a possibility that some cancer cells in the patient will still be present. There are five main types of adjuvant therapy for the treatment of cancer, including chemotherapy,

hormonal, radiation, immune, and targeted therapy. The type of user is dictated by the type and level of cancer, as well as hormone tolerance and involvement of the lymph node (27).

Multidrug Resistance

A major issue in cancer clinical practice is the multidrug resistance (MDR) of tumor cells to chemotherapeutic agents. The enhanced expression of a membrane-associated transport protein such as P-glycoprotein (Pgp) is an important mechanism for acquiring the MDR phenotype in mammalian cells. Pgp is part of the highly conserved adenosine triphosphate cassette-binding (ABC) protein superfamily, which is one of the major groups in the animal kingdom (28).

The functional objective of Pgp in the organs via specialized excretory, secretory, and barrier functions is to afford defense against toxic insults (29). Pgp is commonly expressed in the stomach, liver, and kidney epithelial cells, as well as the brain and placenta endothelial cells.

Generally, the drug aggregation defect present in MDR cells is altered by agents used to antagonize MDR. Although several agents have been tested to inhibit MDR in the hunt for chemo-sensitizers, no chemotherapy user agent exists to date. The modulators of the first generation were not designed specifically for MDR inhibition. Instead, they were discovered by chance, including verapamil, cyclosporine A, reserpine, and the like (30). The undesirable toxicity characteristics of first-generation molecules have been removed in second-generation agents designed after the chemical modification of earlier agents. Such modulators have greater tolerability although they experience volatile pharmacokinetic interactions (i.e., verapamil R isomer, valsopodar, cyclosporine D analog, biricodar, and the like) (31). The compounds of the third generation (i.e., tariquidar, zosuquidar, laniquidar, and the like) have been engineered to be devoid of other therapeutic actions and to give Pgp greater selectivity and specificity. Clinical trials are being performed on many compounds from this group (32).

Biomedical Compounds of Seaweeds and Their Uses

Benthic marine algae or seaweeds are plants that exist either in fresh or brackish water. They are a large group of autotrophic organisms which for oxygen photosynthesis contain chlorophyll. Adaptive osmoregulation processes have been established to retain their osmotic internal pressure and to escape the effects of the resultant turgidity and hypoplasia from changes in their habitat's salinity (33). Marine algae are micro- or macro-algae vegetative organisms, which differ in scale, morphology, and size ranging from 2 μ m to 30 m. They are the predominant aquatic vegetation and are directly involved in habitat complexity, primary ocean development and retention of nutrients, and coastal ecosystems (34).

There have been more records of different natural antimicrobial products in the aquatic compared to the terrestrial environment. A previous study evaluated the source of structurally distinct natural substances with pharmacological and biological activities in marine organisms such as algae (35). As a source of medicinal compounds, marine algae dominate a special position among marine organisms (36) as the possible sources of antibiotic substances. An indication of the existence of antimicrobial active compounds is the synthesis of various metabolites from the seaweed. Macroalgae such as antibacterial active compounds (37) have derived a broad variety of bioactive compounds. Seaweeds have several distinct secondary metabolites with a large variety of biological activities. Compounds with cytostatic, antiviral, anthelmintic, antifungal, and antibacterial activity have been found in orange, brown, and red algae (38).

The seaweed is considered to be the primary source of bioactive compounds with a broad range of biological functions, including antioxidants, antibiotics, and anti-inflammatory compounds (39). Some bio-active materials of macroalgae act against those of pathogenic bacteria in their germination (40). Tuney et al (41) discovered that several species of crude marine algal extracts inhibit pathogenic bacteria. Seaweeds have various medicinal and pharmacotherapy substances while some of the isolated compounds have bacteriostatic and bactericidal characterization (42). Antibiotics have been used to treat different pathogens originating from terrestrial sources and used as therapeutic agents. New compounds have been discovered in the oceans and have economic potential (43).

Efficient cancer care is still missing despite decades of studies (44). In addition, there is a growing demand for new cell-selective anticancer agents with fewer negative impacts, increasing the quality of life of patients (44). Natural products provide a reliable choice when searching for drugs that can aid in the prevention of cancer (45).

Previous research (46) has concentrated on natural products from marine organisms throughout the past several decades primarily because of their broad environment (covering ~70% of the Earth's surface), high biodiversity (95% of the world's biodiversity), and the specific conditions in which these species are present (e.g., at extreme levels of temperature, salinity, and pressure). Among the studied marine compounds, the anticancer potential of extracts and compounds derived from marine algae is particularly exciting. Seaweeds are abundant in bioactive materials which are not found in food sources and terrestrial plants (39). Novel compounds such as fucoidan, alginate, fucoxanthin, polyphenols, and the like can possess unique health-promoting characteristics, including cancer therapy, that can be used in human health applications (47). For their anti-tumor activities, several extract-obtained or slightly distilled products have been examined from various red, green, and brown seaweeds

(48). Gutiérrez-Rodríguez et al (49) reported that several seaweed compounds can be effective anticancer agents.

In response to a variety of evolving pressures in the atmosphere (e.g., salinity, temperature, UV exposure, and light) seaweeds may generate several novel secondary metabolites, which make them the most effective reservoirs of new human treatment materials (50). It has been shown that different compounds derived from a variety of marine algae eradicate or delay the development of cancer. The seaweed has a powerful curing effect on colon and breast cancers, which are the major causes of death rates associated with cancer in women and men (51). Apoptosis was found in cancer cells that were treated with seaweed extracts. Many amassing examples indicate that bioactive compounds derived from seaweeds generate antitumor effects through various modes of action, including the inhibition of tumor cell development, invasion and metastasis, and apoptosis induction in cancer cells (52,53).

In the field of cancer prevention, the ingestion of various types of seaweeds has been recognized to be responsible for the decreased incidence of cancer in Asian countries whose inhabitants traditionally intake a significant amount of seaweeds (51). Based on the findings of a cohort study in Japan, lower lung cancer mortality in males and females and lower pancreatic cancer mortality in males were correlated with seaweed intake in a joint cancer evaluation (54). However, in the above-mentioned analysis, no positive relation was observed between the consumption of the seaweed and prostate cancer, a finding supported by a prospective study of 18,115 Japanese men (55).

Seaweed's Polysaccharides and Cancer Prevention

Polysaccharides seem to be the most commonly studied seaweed-derived cytotoxic compounds (56), and brown seaweeds containing alginate, fucoidan, and laminaran, among others, are the most common source of these bioactive polysaccharides. Sulfated galactans such as agar and carrageenans, which have many promising medicinal properties including antitumor activities are present in red seaweeds (57).

The results of a previous study revealed that alginate, laminaran, fucoidan, and other seaweed polysaccharides have apparent antitumor activities with the ingestion of dietary seaweed fibers capable of preventing cancer development and proliferation in the digestive tract (58). Alginate can cleanse the intestinal tract, increase the level of immunity and the protection of the intestinal tract, and decrease cancer risk. To prevent cancer, laminaran can induce apoptosis, and for several cancers, sulfated polysaccharides such as fucoidan have a wide range of antitumor activities. Direct or indirect antitumor effects are also demonstrated by certain unidentified seaweed polysaccharides (59). The action of an unspecified polysaccharide from *Sargassum confusum* was evaluated in S-180 tumors grown in mice. The improved immune

function was found as measured by boosted the superoxide dismutase and glutathione peroxidase activities and developed thymocytes and splenocytes, as well as declined level of malondialdehyde (60,61).

Alginate is the main polysaccharide from the brown seaweed (62,63). It has a wide variety of bioactivities, including anticoagulants (64), antitumors (65), antivirals, antihypertension, and antioxidants (66). Alginate can also guard against carcinogens by protecting the stomach and intestinal surface membranes from the effects of carcinogenic substances (67). It is impossible for human intestinal enzymes to digest alginate, and therefore, alginic acid in the bowels chelates or makes insoluble heavy metal ions and cannot be absorbed into the body (68). A previous medical trial represented that alginate stimulates the development of the stomach mucous membranes, inhibits inflammation, and removes the mucous membrane colonies of *Helicobacter pylori* (69). Moreover, alginate allows for the restoration of intestinal biogenesis (70,71). Other studies have shown the effects of alginate on fecal microbial fauna, changes in compound and acid concentrations, and health-promoting prebiotic properties, specifically in the prevention of cancer (72,73).

In brown-seaweeds, laminaran is a storage glucan (74) that can serve as prebiotics in addition to its position as a dietary fiber (68). By affecting the composition of mucus, intestinal pH, and the production of short-chain fatty acids, it can also modulate intestinal metabolism. Ecological factors influence the structure and biological activities of laminaran (75).

Furthermore, stronger bioactivities were demonstrated to have sulfated laminaran (75). It was found to inhibit heparanase activity in mouse B16-BL6 melanoma cells and rat 13762 MAT mammary cancer cells. As a result, the ability of the tumor cells to deteriorate heparin sulfate in their extracellular matrixes decreased and an anti-metastatic effect was produced as well. Laminaran sulfate has had an impact on tumor cell proliferation and primary tumor growth *in vivo* at effective concentrations (76). Treatment with *Laminaria* sp has been reported to inhibit the proliferation of colon cancer cells by Fas and insulin-like growth factor I receptor signaling via the intrinsic apoptotic and ErbB pathways, respectively (77).

It also reduced the Bcl-2 family protein, which consists of members that stimulate and control apoptosis by regulating the mitochondrial permeabilization of the outer membrane. By regulating the ErbB-signaling pathway, it is a key step in the intrinsic path of apoptosis, as well as expression and inhibited cell cycle progression (77).

Fucoidan is a sulfated seaweed polysaccharide primarily consisting of l-fucose and sulfate units in addition to small quantities of d-galactose, d-mannose, d-xylose, and uronic acid (52,78). Its biological activities have been investigated as anticancer (79). Some investigations have shown that it can inhibit growth (80) and induce the apoptosis of cancer

cells (81). It can reduce the metastasis (80) and inhibit the angiogenesis of cancer cells (82). It was found that fucoidan can induce apoptosis in a dose-dependent manner in HT-29 and HCT116 colon cancer cells (83). Data from *in vitro* and *in vivo* studies showed direct and inhibitory activity against some cancer cell lines, respectively (84).

Fucoidan can inhibit angiogenesis around cancer cells (85). Proangiogenic cytokine and vascular endothelial growth factor (VEGF) have also been shown to decrease and this has been associated with a substantial decrease in angiogenesis and tumor size in 4T1 tumors *in vivo*. The chick chorioallantoic membrane assay and the gel foam plug assay in mice demonstrated that fucoidan isolated from *Sargassum stenophyllum* has antiangiogenic activity (50). It has been shown that the production of VEGF-A reduced in human umbilical vein endothelial cells exposed to fucoidan isolated from *Undaria pinnatifida* (86).

Seaweed's Polyphenols and Cancer Prevention

Seaweeds include several forms of phenolic compounds because their bioactive components act against grazers, parasites, and epiphytes while for photoprotection (87). The bioactive seaweed polyphenols have a strong antioxidant ability (88) which gives them a role in preventing degenerative diseases such as cancers. Many polyphenolic compounds have been isolated from brown algal organisms (89).

Other Seaweed-Derived Compounds and Antitumor Activities

Carotenoids are tetraterpenoids and expressed by more than 600 recognized natural structural variants of a specific linear C40 molecular backbone (90). They are colorful pigments that can be synthesized in certain non-photosynthetic bacteria. They are involved in photosynthesis, hormonal synthesis, photoprotection, and photomorphogenesis (91). Typically, carotenoids are classified into two classes of carotenes containing only the atoms of carbon and hydrogen and xanthophylls including at least one atom of oxygen (92). B-carotene is the most popular carotene, but the xanthophyll class includes lutein, fucoxanthin, and violaxanthin (93).

In marine algae, carotenoid profiles are used to distinguish gray, brown, and red seaweeds (94). The structure of carotenoids greatly influences their activity as the antioxidant potential enhances by the inclusion of functional groups in the terminal rings. Carotenoids have an antioxidant function that is attributed to their capacity of singlet oxygen to quench and free radicals to scavenge. The mechanism by which oxidative stress-related diseases, including cancer, along with cardiovascular and neurodegenerative diseases are prevented is their antioxidant properties (95). According to Stahl and Sies, there are many forms of cancer that carotenoids can protect against. This is consistent with epidemiological evidence

showing an inverse association between the risk of cancer and the intake diet rich with carotenoids (96).

Fucoxanthin is a carotenoid with a unique property in the hydrocarbon polyene chain, along with the functional groups of allergic bonds and oxygen, including epoxy, hydroxyl, carbonyl, and carboxyl groups (97). It is found in brown seaweeds such as microalgae and macroalgae and has defensive and photosynthetic roles (98). Although its content varies throughout the seaweed season and life cycle, it is the most abundant of all carotenoids found in the brown seaweed (91). The anti-inflammatory, anti-cancer, and antioxidant roles of fucoxanthin have been reported in several studies (99,100). The antioxidant activity of fucoxanthin involves free radical scavenging that is one of the mechanisms behind its anti-cancer effect (93).

In conclusion, the human body had resistance against the traditional treatments of the tumor. Thus, investigators should use the bioactive ingredient of natural products as the seaweed in the treatment. Therefore, our future study will focus on using the brown seaweed extract as an antitumor *in vitro*.

Authors' Contributions

All authors equally contributed to this research.

Conflict of Interest Disclosures

There is no conflict of interests.

Ethical Issues

Not applicable.

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