Seaweeds’ nutraceutical and biomedical potential in cancer therapy: a concise review

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Abstract

Seaweeds have been a food source since ancient times (600 BC) and are still widely used in Asia, mainly in traditional Chinese medicine and Japanese folk medicine. Nowadays, seaweed compounds and extracts have been gaining interest from the biomedical and pharmaceutical market sectors. Seaweeds have been referenced as feasible solutions in finding new potential compounds and therapies in prevention, control, and reduction of cancer development due to the multirole of some bioactive components (e.g. phenolic compounds and sulphated polysaccharides). Moreover, seaweeds are rich in important health-promoting molecules [such as poly and highly unsaturated fatty acids (PUFAs and HUFAs), essential amino acids, vitamins, and dietary fibers] and minerals (calcium, iron, iodine, magnesium, phosphorus, potassium, zinc, copper, manganese, selenium, and fluoride). In this review, the potential therapeutic effects of seaweed in the prevention and treatment of cancer are approached, as well as nutraceutical properties of seaweed to promote cell homeostasis.

Keywords: Seaweed compounds, nutraceutical, bioactive molecules, cancer prevention, cancer treatment
INTRODUCTION

Currently, the world’s population is growing and getting older. Cancer is considered one of the major causes of death in the world\textsuperscript{[1]}. There are multiple types of cancer which are differentiated on the origin of the responsible cell. This disease begins with a cell that is not functioning normally and then starts to grow and multiply uncontrollably, invading, conquering space, and interfering with other tissues, but also spreading through whole human organs depending on the type of abnormality that the cancer cell has\textsuperscript{[2]}. This way, cancer can be classified as carcinoma, sarcoma, lymphoma and leukemia, germ cell tumor, or blastoma\textsuperscript{[3,4]}. During the year 2018, it was estimated 18.1 million new cases of cancer were diagnosed and 9.6 million cancer deaths occurred\textsuperscript{[5]}, making it one of the main causes for human morbidity and mortality. Among the different types of cancer, breast, lung, and the colorectal cancers make up most of the cancer incidence worldwide\textsuperscript{[5-8]}. 

To ameliorate cancer incidence in human population, there is a need to develop new prevention and treatments/therapeutic schemes to avoid the appearance of malfunctioning cells (cancer prevention) and reduce cancer mortality through new biomedical tools for safer and cost-effective treatments\textsuperscript{[4]}. 

Over the past few years, there has been an increase of the associated search for new foods or dietary supplements that can help prevent the occurrence of cancer\textsuperscript{[6]}. For instance, it was observed that some diet strategies, mainly a western diet and respective lifestyle, are positively related to the growing cancer incidence\textsuperscript{[9,10]}. 

The options to treat cancer are surgical management, chemotherapy, radiotherapy, cancer-targeted therapy, and/or immunization therapy. Chemotherapy is the principal therapeutic method employed to treat cancer\textsuperscript{[11]}. Moreover, there is also an enhanced search for new natural compounds that can be used as anti-cancer therapeutics, such as anti-cancer directed activity (through interference in cancer cell lines metabolic pathways), as drug delivery ingredient, or as chemo or radio-protective agent\textsuperscript{[4]}. 

The search for new tools to reduce cancer incidence and to efficiently destroy cancer cells with non-invasive techniques at a reasonable price has increased\textsuperscript{[4]}. This has been achieved through focusing attention towards natural compounds from marine organisms, which can be an interesting source of compounds and have been used in East Asia for a long time (where cancer health problems seem reduced when compared with Western countries)\textsuperscript{[12]}. 

One of the main ingredients used in East Asian food are seaweeds (also known as macroalgae), which are macroscopic (in most part of their lifetime), multicellular, photoautotrophic organisms. They mainly inhabit the seas or brackish water environments. Unlike terrestrial plants, they do not have vascular differentiations, seaweeds are distinguished by the coloration presented in thallus, by red (Rhodophyta), green (Chlorophyta), and brown (Phaeophyceae). Therefore, seaweeds live in multifaceted and dynamic aquatic ecosystems, due to a wide range of variations of biotic and abiotic factors during a day and between seasons\textsuperscript{[13-16]}. 

This way, seaweeds need to be able to adapt for survival in a constantly shifting ecosystem while also being a target as a primary food source. The main factors influencing seaweeds are hydration, temperature, salinity, light, pollutants, nutrients availability, and grazing\textsuperscript{[16-18]}. The gathering of ecological data by the study of seaweed reactions to mentioned factors is important for biotechnological exploitation of seaweeds as depending on their acclimatization to the surrounding environment, they will produce a specific metabolic response\textsuperscript{[19-22]}. Seaweeds are rich in health promoting molecules and minerals, such as sulphated polysaccharides, polyphenolics, terpenoids, flavonoids, pigments, MUFAs (monounsaturated fatty acids), PUFAs (polyunsaturated fatty acids), and HUFAs (highly unsaturated fatty acids), essential amino acids,
vitamins (A, B₁, B₂, B₉, B₁₂, C, D, E, and K), and essential minerals (calcium, iron, iodine, magnesium, phosphorus, potassium, zinc, copper, manganese, selenium, and fluoride). All these are known to be essential for the regular organism functioning.

Seaweeds have interesting compounds for the development of novel food products and of nutraceuticals. A nutraceutical product is a food that has positive effects on human health beyond its nutritional value, thus it might help prevent health problems, such as cancer, arthritis, diabetes, autoimmune diseases, ocular diseases, and cardiovascular diseases. These benefits result from the many bioactivities seaweeds and their extracted compounds can possess: anti-cancer, anti-fungal, anti-inflammatory, anti-cholesterol, anti-pruritic, anti-allergic, anti-viral, anti-bacterial, antioxidant, neuroprotective, chemoprotective, immunomodulatory, and hepatoprotective.

However, seaweed potential application in cancer treatment is not strictly preventive. There are studies that already support the biomedical potential of isolated compounds when applied in various cancer therapeutic solutions, such as anti-cancer compounds (by inhibition of cancer cell growth and invasion, but also anti-mutagenic, anti-metastatic, and apoptosis induction potential), drug delivery system, and chemoprotective agent.

In this review, the main subjects addressed are seaweeds’ role in cancer development prevention and the potential of seaweed compounds in cancer treatment from a therapeutic and nutraceutical point of view.
Data was collected from online databases, mainly Web of Science, Google Scholar, and PubMed, considering research articles, books, chapters, and reviews. The selected topics included the following combinations: seaweed, macroalgae, cancer, tumor, carcinogenesis.

After critical analysis of this thematic, the review focused on the seaweed nutraceutical potential and existing studies prospecting seaweed consumption as a food supplement and its potential correlation with cancer incidence. Moreover, the review also analyzes the potential of seaweed compounds in cancer treatment and the road that these need to go through before clinical application. The review does not focus on pre-clinical studies nor compounds screening, as there are already recent reviews which are excellent compendiums of the seaweed compounds with anti-cancer activity against various types of cancer cells\cite{4,34,41,43,45}.

**SEAWEEDS AS CELL HOMEOTASIS PROMOTERS**

The incorporation of seaweed in the basis of a daily diet has been adopted by ancient civilizations in the East Asian countries\cite{46,47}. Moreover, several coastal countries worldwide have records of seaweed consumption\cite{48,49}. Despite the recent global trend regarding the introduction of seaweed as a health promoter supplement, these sea vegetables have been used for a long time by Asian populations as a flavor enhancer agent in food products, drinks, and beverages\cite{47,56,55}.

Despite the reluctance by some cultures to integrate seaweed in their daily diet due to metal bioaccumulation ability from macroalgae, studies showed that the trace element content of highly consumed species does not exceed the values referenced as safe for consumption, according to European Food Safety Authority (EFSA) threshold, as reviewed by other authors\cite{52}.

Figure 2. Seaweeds’ main nutraceutical and therapeutic applications in cancer treatment research.
Among the several benefits of seaweed incorporation in human daily diet, researchers demonstrated that their consumption is directly related with lower probabilities of cancer development\(^{[47]}\). For instance, researchers found evidences that, among the East Asian population, people with a regular seaweed consumption habit reduced the risk of colorectal cancer development by half\(^{[35]}\). On the other hand, people with a meat and processed food based diet and occasional seaweed consumption, had higher risk of developing this type of cancer\(^{[53,54]}\).

In fact, in Western countries, higher cancer incidence was recorded when compared to Japan\(^{[5,8,55,56]}\). With the increase of food availability and processed food commerce throughout developed countries, a general adoption towards fast meals is being observed. For instance, among the Japanese population, increased consumption of red meat and dairy products concurred with a period of higher incidence of chronic diseases\(^{[57,58]}\).

To corroborate this hypothesis, researchers have been highlighting seaweeds’ anti-cancer bioactivities through *in vitro* and *in vivo* experiments, while also observing and reporting that regular seaweed intake has been directly related to lower mortality rates among patients diagnosed with lung or pancreatic cancers\(^{[59]}\).

On the other hand, there is a need to certify the seaweed quality before commercialization due to potential problems of high heavy metals and iodine concentrations\(^{[47]}\). To surpass this issue, there is a need to develop legislation to support seaweeds safe consumption; for example, the FDA (USA) and EFSA (EU) are active entities in assuring seaweed minimum quality for the food market\(^{[35,60]}\).

### Seaweed compounds profiles: nutraceutical effects

Seaweeds are in fact a food product that can provide essential macro and micronutrients, as well as trace elements, which are pivotal to maintain human cell homeostasis. However, it is necessary to consider that seaweed biochemical profiles differ according to species, geographical location, tidal exposure, season, physico-chemical composition of the water, or even with the seaweed processing techniques\(^{[17,61-63]}\). Nevertheless, they are considered a nutraceutical and valuable resource due to their richness in proteins, minerals, vitamins, polysaccharides, pigments, and phenols\(^{[64-66]}\).

Diseases such as diabetes, obesity or cardiovascular problems are often associated with a high fat diet\(^{[6,67,68]}\). Particularly, the increase of total cholesterol and low-density lipoprotein cholesterol (LDL-C) are the main risk factors that promote the development of cardiovascular diseases\(^{[69]}\). Studies highlight the importance of including food products rich in polyunsaturated fatty acids in our diets on a daily basis to boost the immune system\(^{[70]}\). Furthermore, lipids are essential macronutrients to the proper performance of the human body. These compounds integrate several metabolic pathways, such as energy supply, hormones and membranes synthesis\(^{[71]}\). These compounds are also important for vitamins transport and absorption\(^{[6,68]}\). In this context, seaweeds are a well-known source of essential fatty acids, which the human body is not able to synthesize, such as omega-3 (n-3) and omega-6 (n-6)\(^{[72,73]}\).

A diet poor in proteins can lead to the development of several diseases, such as hyperphagia or thermogenesis, which are associated with obesity\(^{[74-76]}\). Therefore, it is important to have a varied diet with significant protein uptake. Seaweeds can synthesize all the essential amino acids, which the human body is not able to produce and needs to take from the diet, namely histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine\(^{[63,77-79]}\).

Proteins are extremely important molecules for the good function of the human body. These macromolecules are key elements in skin, bones, muscles, and cartilage regenerations as enzymes, hormones, or antibodies precursors\(^{[62,77]}\).
Seaweed polysaccharides are a promising dietary supplement due to their chemical and structural characteristics. Since the human body does not possess enzymes capable of degrading some of these long-chain polymers (polysaccharides weighing over 120 kDa), they are considered healthy sugars that satiate, but are not absorbed. In this context, seaweed polysaccharides such as agar, carrageenan, and alginate are health promoters, preventing diseases related with obesity. Moreover, researchers already demonstrated that commercially available products containing carrageenan can be an anti-cholesterol agent. Several studies also highlight pharmacological bioactivities of these natural compounds, such as antioxidant, neuroprotective, anti-bacterial, or anti-inflammatory. Fucoidan and other low molecular polysaccharides can be absorbed in the gastrointestinal systems. In fact, seaweed polysaccharides behave as dietary fibers known to stimulate intestinal mucus production and thickness, providing protection against toxins and carcinogenic compounds.

Micronutrients, such as minerals (calcium, magnesium, phosphorous, or potassium), trace elements (manganese, iron, zinc, or iodine), and vitamins (A, D, E, and K), even in low amounts, are crucial substances for the human body. The lack of these compounds is responsible for several diseases, such as anemia, xerophthalmia, osteoporosis, and increases the risks of developing cancer and cardiovascular diseases. These compounds are important structural elements of the skeleton and are also involved in regulatory functions of the human body, such as oxygen transport or neurotransmission.

Undernourishment prevention is a complex challenge in which it is necessary to ensure a balanced and varied diet, rich in all key nutrients needed to the good functioning of the human body. Seaweeds exhibit a rich nutritional content, being rich in several micronutrients, such as iodine, magnesium, sodium, and potassium. Moreover, seaweeds are also a source of vitamins, namely A, B, C, and E, which are essential elements in a healthy diet. Therefore, seaweeds can be useful natural and nutraceutical food resources that can contribute to a healthier diet and potentially help prevent cancer by contributing to better nutritional balance.

Seaweeds are natural sources of pigments, such as phycocyanin, phycoerythrin, β-carotene, α-carotene, fucoxanthin, astaxanthin, canthaxanthin, zeaxanthin, and lutein. These compounds are known for their antioxidant bioactivity which is privileged on cancer prevention as free radicals are recognized as a sign of stress or imbalance, thus contributing to potential cancer development. In fact, these compounds are already widely used in food and cosmetic industries as natural colorants. However, they are also applied in medical assays as biomarkers.

Many studies focus on the study of pigments’ bioactivities, revealing interesting biomedical applications, such as chemotherapeutical and neuroprotective agents, tumor suppression activity, anti-inflammatory, and anti-irradiative effects. For instance, phycobiliproteins have revealed their nutraceutical and pharmacological potential through their antioxidant, anti-inflammatory, antitumor, anti-enterovirus, and hepatoprotective bioactivities. Moreover, investigation findings reported that carotenoids are highly valuable compounds with potential pharmaceutical application due to their antioxidant, anti-inflammatory, and anti-cancer bioactivities, reducing the risks of several diseases affecting humans.

Phenolic compounds are secondary metabolites derived from seaweeds, likewise phlorotannins, bromophenols, flavonoids, phenolic terpenoids, and mycosporine-like amino acids, being considered bioactive molecules. These metabolic products are normally produced by seaweeds as response to environmental and ecological stress factors, such as herbivory and ultraviolet radiation exposure. Research has showed that the mentioned compounds have wide biotechnological applications, such as anti-inflammatory, anti-bacterial, anti-viral, anti-allergic, anti-diabetic, antioxidant, anti-photoaging,
anti-pruritic, hepatoprotective, hypotension, neuroprotective, and anti-cancer properties\textsuperscript{129-142}. These compounds can interact with cell receptors, enzymes, and proteins, enhance the immune system, and exhibit several biological activities that are important to maintaining good health\textsuperscript{143}. All of the mentioned characteristics and properties of these compounds make them suitable candidates for the development of novel pharmacological, cosmeceutical, and nutraceutical products\textsuperscript{19,33,141,144,145}. For this reason, phenolic compounds can be employed as health agent promoting food supplements and even increase food products shelf-life\textsuperscript{146,147}.

Furthermore, seaweed sterols, such as desmosterol, cholesta-4,6-dien-3-ol, and cholest-5-ene-3,7-diol\textsuperscript{148-150} are essential molecules for structural and hormonal function, with antioxidant, anti-viral, anti-fungal, and anti-bacterial bioactivities\textsuperscript{33,34,126,151}.

**Seaweeds intake and cancer relationship: a nutraceutical effect?**

Several epidemiological records, in most of the cases around the world, have proposed that cancer is an avoidable disease. The causes of cancer development normally share pathogenic mechanisms such as DNA damage, oxidative stress, and/or chronic inflammation\textsuperscript{47,152}. Currently, further studies aimed to understand cancer development and its prevention concluded that mitigation measures depend on better daily choices, such as avoiding excessive UV light and radiation exposure, reducing alcohol consumption, not smoking, and choosing healthy food diets [Figure 3A]\textsuperscript{153}.

As mentioned before, in some countries, mainly in East Asia, there is a tradition of seaweeds consumption, which, as previously referred, are rich in biological active metabolites and other macro and micronutrients that regulate the good function of the human body in a recommended daily intake\textsuperscript{153}. An example are brown seaweeds, which are a very popular food in Japan. It was demonstrated that 5 g per day of dried seaweed is well tolerated in the human organism, and in a traditional Japanese diet, the average daily seaweed intake is normally around 4-7 g of dried seaweed\textsuperscript{154}.

Minami et al.\textsuperscript{155} demonstrated that seaweed consumption decreased the patient mortality with colon and rectal cancer using cancer patients in Japan. This could be due to the seaweed polysaccharides, which in the human gastrointestinal system behave as dietary fibers. Seaweed polysaccharides can alter the microbiota structure in the human gastrointestinal tract\textsuperscript{156-158}. A high fiber diet ingestion enhances the microbiota population to produce short-chain fatty acids, which have demonstrated to have anti-cancer and anti-inflammatory effects\textsuperscript{159-161}. This type of modulation of the gastrointestinal microbiota by dietary fibers could have a positive impact in the prevention of stomach cancer\textsuperscript{162}. This type of benefit from seaweed intake also appears to be related with the consumption of *Laminaria/ Saccharina* sp., or other brown seaweeds (*Undaria pinnatifida*) that can help the gastrointestinal system and prevent the initiation of breast cancer or its development by endogenous human factors\textsuperscript{163}. This can be due to the iodine content, among other compounds, in brown seaweeds\textsuperscript{164,165}. Funahashi et al.\textsuperscript{166} reported that consumption of *U. pinnatifida* [Figure 3B] demonstrates high suppressive effect against mammary cancer in an *in vivo* rat model, even at a low percentage (seaweed flakes, at 1%-5% dry weight as a supplement integrated in the feeding). However, these results are only from rat models and more detailed information is still needed regarding human trials\textsuperscript{165}. Nevertheless, this assay with *Laminaria/Saccharina* sp. showed a chemo-preventive pattern against cancer incidence that might be promising in the future\textsuperscript{166}. However, there is explicit risk that overdosage can have negative effects. Teas et al.\textsuperscript{93} reported that, among women from the USA, consuming *U. pinnatifida* revealed positive effects against breast cancer. The seaweed intake lowered urokinase-type plasminogen activator receptor (uPAR), an important receptor to the cell homeostasis, participating in various metabolic pathways which, when in high concentration, can increase abnormal cell function and develop into a cancer\textsuperscript{83}. The observed seaweed intake from this study (5 g of encapsulated seaweed powder per day) lowered the level of the uPar up to 50% of the initial concentration in urine\textsuperscript{99}. This supplement
can be useful for women in the premenopausal period to reduce the potential development of breast cancer, mainly due to iodine concentration in brown seaweeds\textsuperscript{154}. Also to be noted, 5 g of dried seaweed (\textit{Undaria} sp., \textit{Laminaria} sp., \textit{Saccharina} sp., and \textit{Alaria} sp.) have demonstrated to increase the thyroid stimulating hormone, yet, the increase was considered small and not biologically relevant\textsuperscript{154}. Nevertheless, high concentration of iodine in seaweed is considered a risk towards development of thyroid cancer\textsuperscript{47}. In this case, the dosage is the main factor of the benefit or problematic of seaweeds intake\textsuperscript{47,167}. From another study in South Korea, \textit{Undaria pinnatifida} intake among women (362, between 30-65 years old) did not correlate to a lower breast cancer incidence\textsuperscript{168}. However, in the same study, the high intake of \textit{Porphyra/Pyropia} sp. decreased the risks of breast cancer [Figure 3C]\textsuperscript{168}.

To consider seaweeds as nutraceutical ingredients, there is a need of more assays to fully understand their potential as preventive sources against cancer and other human diseases\textsuperscript{169}. Even though more work is necessary, the reviewed results reported here can be considered a positive support towards classifying seaweeds as favorable nutraceuticals for humans against cancer incidence. In future work, to start understanding the true nature of this seaweed potential against cancer incidence, studies should start considering the nutritional profiles. Nutritional profile of the seaweed content used, as previously mentioned, can vary greatly among the same species depending on the conditions it grew or was harvested and processed\textsuperscript{35,52,170}. This could bring some clarification in situations like the reported \textit{U. pinnatifida} studies in USA and Korea, which reported opposite results.

**BIOMEDICAL POTENTIAL OF SEAWEED COMPOUNDS**

Seaweeds have high nutritional potential with nutraceutical potential, as previously demonstrated. However, seaweed isolated compounds have been studied and reveal a wide range of bioactive potential, such as anti-bacterial, anti-viral, anti-allergic, anti-diabetic, antioxidant, anti-photoaging, anti-pruritic, hepatoprotective, hypotension, neuroprotective, and anticancer properties\textsuperscript{130,133,141}. Moreover, there are diverse pharmaceuticals and new drugs with seaweed compounds as active agents with the most known being phlorotannins to treat cardiovascular diseases\textsuperscript{171}, or secondary compounds to encapsulate or stabilize the active agent, for example, the brown seaweed polymer alginate\textsuperscript{172}. However, the most explored seaweed compounds in the biomedical area are phenolic compounds, pigments, and polysaccharides.

**Phenolic compounds**

Phenols are secondary metabolic products of seaweed, which are a complex category of chemical compounds that are water-soluble compounds and which share a hydroxyl group connected to an aromatic hydrocarbon group\textsuperscript{173}. Phenols can be classified into basic phenolic compounds according to the number
Pigments
Three kinds of pigment groups can be produced by seaweeds as photosynthetic organisms: chlorophylls, carotenoids, and phycobiliproteins. The color of the algae determines the pigments in them. The presence of chlorophylls a and b causes the green color. Phycobilins, such as phycoerythrin and phycocyanin, are responsible for the red color. Where the chlorophylls a, c1, and c2, b-carotene, and fucoxanthin are usually the pigments present in brown seaweeds[173].

These isolated compounds have been documented with anti-bacterial, anti-inflammatory, neuroprotection antioxidant, and anti-tumor effects[170]. And, these compounds are being studied to be applied as fluorescent markers in the biomedical field[113].

Polysaccharides
In the present biomedical field, seaweed-derived polysaccharides with specific structural and functional characteristics have acquired special research focus[174]. Researchers and industry have been using the beneﬁc inherited characteristics of seaweed polysaccharides, such as those of a biologically tunable, biocompatible, biodegradable, reusable, and non-toxic nature, to design new biomaterial for drug delivery, tissue engineering, and wound dressings[172,174]. Seaweed polysaccharide are therapeutically effective with controlled distribution[174]. Especially with alginate, an anionic polymer without high bioactivity and unlike other seaweed polysaccharides like fucoidan, which is an anionic sulfated polysaccharide extracted from brown seaweed, which possess a wide range of bioactivities: anti-inflammatory, anti-oxidative, anticoagulant, and antithrombotic effects[175]. Fucoidan has been widely researched over the past decade to be applied on drug and gene delivery systems and diagnostic microparticles[175].

From red seaweed, carrageenan was used as a popular medicine from ancient times to ameliorate cough and common colds and this has been conﬁrmed by in vitro and in vivo assays. This ability is primarily derived from the function of carrageenan to suppress blood platelet aggregation (i.e. anticoagulant activity)[6,176]. Different carrageenans excel in other demonstrable bioactivities such, anti-tumor, anti-viral, and immunomodulation activities, being commercially exploited due to their anti-viral properties[177,178]. Agar is applied in the biomedical field as a bulking and suspension component in drug solutions and in prescription products, but also as anti-coagulant agents and as a laxative in capsules and tablets. Moreover, they are also used for development of new biomedical techniques of analysis and characterization[178-180].

Other compounds with biomedical interest
There are compounds isolated from seaweed which have a general lack of published studies[181]. Fatty acids can play an important role in the development of new biomedical solutions for immunomodulation drugs and in the treatment and prevention of many neoplastic, ocular, cardiovascular, neurodegenerative, and autoimmune disorders[175,184]. Seaweed sterols are precursors of plant and animal hormones and also have many bioactivities, such as antioxidants, antivirals, anti-fungal, and anti-bacterial[33].

Although there is this seaweed biomedical potential, only a reduced number of seaweed compounds are already being applied in the biomedical field[34,44,175]. As the biomedical interest in seaweed is fairly recent, there is need for more research and development around other potential seaweed compounds for this field.
SEAWEEDS COMPOUNDS IN CANCER THERAPY/THERAPEUTICS: A POTENTIAL TO EXPLORE

When cancer develops, there is a need to take immediate action to destroy or reduce its impact. Thus, a request in the search for new therapeutics is necessary as what is available does not seem to be successful enough. This is mainly due to available treatments being very harmful (with wide range of negative secondary effects) and actual efficiency of the most common techniques being low. Only some very expensive techniques seem to have low secondary effects with high efficiency in destroying cancer cells [18,182-184]. Recent research has been focusing efforts in the discovery of compounds which are cost-effective, efficient and with low or absence of secondary effects [182]. In this case, there are several molecules derived from marine organisms proven to be beneficial in various stages against cancer proliferation and also against various different human cancer lines [182]. However, from discovery to final product, it is a long step with various clinical stages and, so far, seaweeds anti-cancer potential has only been evaluated through what can be considered pre-clinical stage studies (in vitro and in vivo assays). Nevertheless, there are already some components, mainly sulphated polysaccharides (fucoidan/laminarin), that are in clinical stage studies and with promising results which might end with new therapeutic agents in a few years [182]. In vivo assays are mainly based in rodent model systems and results might differ in humans. Therefore, there is the urge for new study models with improved assay methodologies for a better assessment of potential new therapies where new in vitro assays could be a solution along with tissue engineering [18]. Clinical trials with patients are risky due to the poor and life-threatening health status of cancer patients in which trials with experimenting components need to be critically analyzed due to the potential interaction with the cancer treatment already in course [6]. This is why experimental studies in course among Cancer Treatment Medical Facilities are toned to guarantee patient health status monitoring and can only use new therapeutics which passed the pre-clinical and safety assays [186,187]. For example, the Bis(2,3-dibromo-4,5-dihydroxybenzyl) ether compound isolated and characterized in red seaweeds, is now chemically synthetized for further studies [188,189,190]. This compound has demonstrated anti-angiogenesis properties in vitro and in vivo (in zebrafish embryos), by decreasing the HUVEC (human umbilical vein endothelial cells) cells proliferation, migration, and also tube formation [188]. These assays, together with the fact that the compound itself displays a different chemical structure than other anti-angiogenesis therapeutic agents, support the potential for further studies towards cancer [188,190].

Bioactive compounds against cancer

The development of cancer (carcinogenesis) is a multi-step process described by diverse marks, such as sustention of proliferative signaling, evasion of growth suppressors, resistance to cell death, activation of invasion and metastasis, and induction of angiogenesis [191]. The wide range of molecular targets and carcinogenesis mechanisms allows a further exploitation of natural anti-cancer agents efficient in one particular step of all core steps from carcinogenesis [192]. The main targets where anti-cancer therapeutics usually work could be: preventing cell resistance to apoptosis or cell cycle checkpoints modifications, directly protecting DNA from damage or enhancing DNA repair mechanisms, and/or protecting against oxidative stress and reactive oxygen species (ROS) [193,195-199]. Natural compounds have gained interest due to the increase of cancer resistance and undesirable side effects among synthetic choices. Therefore, natural compounds could integrate cancer therapies, targeting one of the carcinogenesis pathways without cytotoxic effects to the healthy cells, and combined with other types of already applied synthetic drugs, reducing side effects and potentially enhancing the therapeutic outcome [192]. In this field, there are already very incisive reviews with high volume of screened potential anti-cancer seaweed compounds, such as phenols, sulphated polysaccharides, halogenated compounds, peptides, pigments, fatty acids, among other types of compounds, making them excellent bibliographic compendia of seaweed compounds assayed and tested in vitro and in vivo in role models against various cancer cells types [Table 1].
According to compound chemical characterization, for example, the polysaccharides activity depends mostly from the sulphation degree and sulphate groups position, which allows the categorization of different types of carrageenan, such as α, β, γ, θ, τ, κ, λ, μ, and ν.

As scientific evidence shows, there are various types of seaweed compounds that demonstrate activity against cancer through induction of cell death and making them anti-proliferative agents of carcinogenic cells.

Several studies highlight carrageenan potential for cellular inhibition, exhibiting cytotoxic effects in carcinogenic cells. For instance, κ- and λ-carrageenan showed inhibitory activity against human cervical carcinoma cells (HeLa), with an IC_{50} of 550.8 μg/mL and 475 μg/mL, respectively.

In some cases, the mechanism of action is not completely understood or revealed, which makes it dubious how the compound reacts and how it can be exploited in further assays. However, when described, seaweed...
compounds can act in different pathways of the evolution of cancer, as in proliferative signaling, cell metastasis, cell cycle, resistance to cell death, evasion, angiogenesis and evasion of growth suppressors\(^\text{[15]}\). They can also act in only one pathway or in various pathways simultaneously\(^\text{[207-210]}\).

However, between the discovery of the anti-cancer bioactivity of a compound up to the potential clinical trials, further studies are necessary to fully understand action mechanisms, benefits, and risks. This significantly reduces the potential targets into a restrictive range of compounds that can become a chemotherapy agent\(^\text{[135,211,212]}\). Moreover, these can be compounds present in very low content among seaweeds, increasing the difficulty to produce, isolate, and purify.

One of the main problems in preliminary screenings is the heterogeneity of the experimental conception and design within research studies, which do not clarify compounds and concentrations. This delivers a negative impact for further exploration due to the rigorous protocols to follow in clinical assays. Moreover, this heterogeneity can be disastrous for the knowledge acquisition and selectivity of the best compounds to be further assayed\(^\text{[16]}\). However, the US National Cancer Institute (NCI) established a standard protocol for the anti-cancer activity preclinical evaluation of compounds\(^\text{[213]}\). Such US NCI standard parameters turned necessary include evaluation of drug cytotoxic effect, drug absorption, distribution, activation, half-life, metabolism, elimination, and minimum adverse effects\(^\text{[41]}\).

Seaweed polysaccharides can also be a key to create hydrogel-based tumor models for cancer research, where it is important and vital to simulate and mimic the dynamic tumor extracellular matrix, to give the best real input of an anti-cancer drug in the affected area\(^\text{[214]}\). They could be used for a model support structure, mainly non-anionic and non-reactive calcium and/ or sodium alginate\(^\text{[214]}\). This methodology tries to substitute in vivo assays which use live animal models where the natural microenvironment of human cancer is not totally achieved.

Seaweed immunotherapy compounds against cancer
Seaweed compounds also enhance the immune system response against cancer. They have an immunomodulatory effect that is described in Table 2. The theory behind cancer immunotherapy is an activation of the immune system so it can attack and destroy target tumor cells through identification of cancer antigens\(^\text{[215]}\). The development and evaluation of new agents is important to develop safe and more effective therapies for cancer treatment\(^\text{[216,217]}\). Seaweed compounds are being described as immune regulators and stimulators which could activate the human immune cells and enhance the body’s immune function\(^\text{[218]}\).

Even as food/feed supplement, seaweed compounds show the ability to enhance the immune response to an abnormal situation in the human body, preventing or delaying the development of cancer growth\(^\text{[199,219]}\). Mainly, the response pathway is believed to be through the induction of NK and T-cell responses to the abnormal behavior. Moreover, seaweed compounds have a modulatory and protective effect in the macrophages which help prevent cancer metastasis\(^\text{[200,222,225]}\). The presented Table 2 demonstrates the potential of seaweed compounds (mainly polysaccharides, as the seaweed most known compound type) as a new and useful molecule to apply in cancer immunotherapy, in the future\(^\text{[199,222,226]}\). Nevertheless, further studies are needed until it is possible to have a safe compound for immunotherapy.

Drug delivery system
Active anti-cancer agents are commonly not administered in pure state, but rather as part of a prescribed amount where the active compound is regularly combined and encapsulated with other agents (excipients). Seaweed polysaccharides are already used in conventional drug capsulation. These can be for oral intake or intravenous therapies\(^\text{[217]}\). They can act in cancer therapy as drug delivery agents as suggested by studies
with agar, carrageenan, alginate, and fucoidan. Seaweed polysaccharides have gained interest in this topic due to the already available know-how as they are easy to obtain and purify, cost effective, non-toxic, biodegradable, biocompatible, and easy to work with. Also, using natural hydrophilic seaweed polysaccharides to encapsulate hydrophobic anti-cancer agents is practicable, and can diminish side effects and the dispersion of the chemotherapy agents in the human body, thus amplifying the therapeutic efficiency and efficacy.

A study demonstrated the prospective effect of a hybrid hyaluronic acid-agar-based hydrogel in drug delivery in intravitreal treatments. Moreover, agar injectable hydrogel with MoS2/Bi2S3-PEG (MBP), doxorubicin (DOX) can be administered in the intra-tumor area when heated. Y et, when agar-based hydrogel is cooled in the administered area, it forms a static hydrogel reducing the area where the active compounds are acting.

Kappa carrageenan was tested to transport curcumin in the treatment of lung cancer cells (A59) and the drug delivery system design was proven efficient. Results demonstrated that the curcumin associated to a carrageenan drug delivery was more active against the cancer cells than curcumin in its free form. Similarly, Lai et al. used hybrid fucoidan - Poly(lactic-co-glycolic acid) to encapsulate a hydrophobic anti-cancer compound (docetaxel).

Demonstrating the potential of seaweed polymers as drug delivery systems that can concentrate and perform a controlled release of anti-cancer compounds might also contribute to the optimization of anti-cancer therapy. Alginate-based hydrogels can incorporate doxorubicin and control-release the drug up to 20 days with high efficiency in vivo in mouse models.

Alginate-based drug delivery systems can arrange self-assembled structures, such as gels in aqueous media, thus having high potential in several drug delivery applications, such as anti-cancer agent transport. The thermo-sensitive alginate hydrogels are already well investigated to be applied in drug delivery systems, such as a drug delivery system in which part of the alginate-based gel swelling could be regulated through temperature variations, leading to on-demand modulation of drug-release. This can reduce the impact of the anti-cancer agent in the organism and enhance its efficacy to treat the cancer. These alginate-based gels can be loaded with simultaneous multiple drugs or sequential pre-determined delivery, where the incorporation and release kinetics need to be carefully analyzed.

Table 2. Seaweed compounds with immunomodulatory effect in cancer

| Source (or Marine Algae) | Compound | Cancer | Type of assay | Concentration | Possible pathway | Resulting outcomes | Ref. |
|--------------------------|----------|--------|----------------|--------------|------------------|--------------------|------|
| Undaria pinnatifida sporophylls | Fucoidan | Leukemia A20 cells | In vivo mice | 1% of the feed 10 day before the inoculation and 40 days after 50 mg/mL | T-cell mediated and NK cell response | Tumor destruction by immune response | [219] |
| Sargassum hemiphyllum Oligo-fucoidan | HCT116 | In vitro | DNA damage response and cell cycle checkpoint | Prevent HCT116 tumorigenicity and regulate the cancer cell death | 21-33 mg/mL | [220] |
| Sargassum sp. | Fucoidan | SMCC-7721, Huh7, and HCCML3 liver | In vivo mice and in vitro | Deactivates the integrin αvβ3/SRC/E2F1 signaling pathway Increase tumor-infiltrating M1 macrophages, and proinflammatory cytokines | Antimetastatic | [221] |
| Nd (Sigma-Aldrich (cat.22049)) α-carageenan | Melanoma B16-F10 and mammary cancer 4T1 | In vivo mice | Injected every two days intratumorally at a dose of 50 mg/kg | DNA damage response and cell cycle checkpoint Prevent HCT116 tumorigenicity and regulate the cancer cell death | Inhibit tumor growth | [222] |
| Laminaria digitata | Laminarin (from B16-ovallbumin melanoma tumor) | In vivo mice | 25 mg/kg | Enhance the production cytotoxic T lymphocyte activation and interferon-γ production Inhibit tumor growth and metastasis | Inhibition of tumor growth and metastasis | [223] |
| Fucus vesiculosus | Fucoidan | Human hepatoma cell line MHCC-97H | In vitro | 100 ng/mL | Macrophages M2 anti-inflammatory reduction | Inhibition of tumor cell migration | [224] |

Source: Cotas et al. J Cancer Metastasis Treat (2021) 7:13, DOI: 10.20517/2394-4722.2020.134
Seaweed polysaccharides are the most used seaweed compounds in this area due to existing industrial and commercial exploitation. They can be low-cost, since they are chemically stable in various seaweed species commercially exploited. In terms of applicability, they are easy to apply and can be modified to different objectives besides being natural compounds, thus biocompatible.

**Radiotherapy and chemoprotective agents**

Protective agents are very important to protect the body against side effects of radiotherapy and chemotherapy due to debilitating effects of these types of treatment which have harmful effects in healthy cells. Some of the common problems can be immunosuppression and nauseas. The protective agents are administrated to selectively protect healthy cells from the dangerous and harmful effects of radiotherapy and chemotherapy agents.[240]

Among seaweeds, there are already studies that support a potential exploitation as protective agents with phlorotannins being the most studied[110]. The phlorotannins extract from *Ecklonia cava* has demonstrated a protective effect of healthy cells against radiation-induced injury and ROS-based injuries[241]. The phlorotannins eckol, dieckol, and triphlorethol-A, extracted from the *Ecklonia* genus, showed a multi-role in protection against γ-irradiation, thus revealing an interesting potential as a protective agent in radiotherapy[36-39,242]. The mechanism of protection is designed to prevent DNA damage and lipid peroxidation.

Phlorotannins antioxidant activity is higher when compared with natural food used antioxidants, ascorbic acid, or tocopherol[243,244], indicating an action against oxidative-induced stress and inflammatory diseases[245]. Moreover, it has been demonstrated that phlorotannins can be used as a protective agents against the toxicity of drugs in humans without diminishing the drug’s effects, but fading the harm of the drug-based toxicity[246].

Therefore, seaweed compounds can have a role in protecting the organism against the secondary effects of the therapeutics that create harmful effects in healthy cells, and, moreover, the consumption of certain species of seaweeds can have a positive effect in maintaining the organism status quo. However, there is need for further studies to support and create new protection schemes that diminish the harm of the most aggressive anti-cancer therapeutics.

**Seaweed compounds in pre-clinical and clinical trials to treat cancer**

Chemotherapy is the most commonly chosen therapeutic technique for cancer treatment and is the one that can have the most adverse effects in healthy cells. Nowadays, there is an enhanced quest for natural compounds due to natural existent compounds which have normally low secondary harmful reactions when compared to synthetic alternatives. This search has already given results with various molecules used in clinical cancer treatment, for example camptothecin (extracted from the tree *Camptotheca acuminata*) and taxol (isolated from the tree *Taxus brevifolia*)[247].

In seaweeds, the development of anti-cancer therapeutic agent is in the beginning, nevertheless, there are already some compounds which are patented and in clinical trials[6].

At a pre-clinical stage with some relevance and also some complication, there is fucoidan, a low molecular weight sulphated polysaccharide extracted from brown seaweeds. The problem holds on the difficulty to isolate only one fucoidan present in the seaweeds, but, as already demonstrated, it possesses a high anti-proliferative, antiangiogenic, and anti-cancer capacity[199,248,249]. That demonstrates how fucoidan has multiple roles against cancer cell growth and proliferation. However, this molecule varies its composition among species, but also depending on seasonality, geolocation, and maturity[199,250]. Moreover, fucoidans
can also have impact in reducing drug resistance by cancer cells, being a possible tool to enhance the chemotherapy compounds when cancer cells have gained resistance [255]. Thus, fucoidan can be used as an adjuvant agent in chemotherapy [199]. This compound is one of the main compounds explored as a novel anti-cancer therapeutic, due to its low toxicity and being commercially approved by different authorities around the world as a food nutritional supplement [248,249]. To be a pharmacological potential agent, there is a need to characterize and develop a method to guarantee the stability of the extracted fucoidan to do further pre-clinical studies and clinical trials [255]. In the absorption assays, fucoidan detection and measurement through oral administration is minor, so the concentration of fucoidan is inaccurately measured [255]. This way, fucoidan has not up till now been certified as a drug, consequently large-scale clinical trials cannot be carried [255].

A depsipeptide denominated Kahalalide F, which is isolated from green seaweed Bryopsis sp., is patented for application in the human lung cancer and is being assayed in advanced clinical trials for the treatment of liver cancer. This compound demonstrated selectivity towards cancer cells, which creates more interest in testing against various types of cancer to check the range of the potential usage [6,258,259]. At a similar level, fucoxanthin, has anti-cancer activity and can be used as a drug delivery agent, but there is lack of complementary information to go to the next level [40]. There are several clinical assays with fucoidan as a food supplement and as a therapeutic agent, but the number of patients is low (maximum 54 patients) [199]. These assays demonstrate good results of fucoidan in chemoprevention as an adjuvant therapy to lower the therapeutic drug secondary effects [255-257].

In cancer treatment, there is an old compound, based in brown seaweed phycocolloid (Algasol T331), which was used at clinical stage studies with human patients [261]. The benefits of this compound was in the post-surgery management and after radiotherapy of oncology patients [261]. The compounds’ main effects were protecting the human body and allowing it to recover faster from more intensive and harmful cancer therapy, mainly in the recovery of hematic function and reduction of asthenia [261].

However, there is a long road from the screening of bioactive compounds which have anti-cancer properties or permit to use in new therapies, until clinical applications. At the moment, seaweed compounds are mainly in pre-clinical assays so that the best compounds can be tested in clinical trials (pre-clinical - Tables 1 and 2; clinical - Table 3) [18].

### Table 3. Actual compounds from seaweeds that are already in use or in advanced clinical trials

| Source             | Compound     | Type of cancer                             | Activity                                      | Resulting outcomes                                                                                                                                                                                                 | Ref.                           |
|--------------------|--------------|--------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Brown seaweed      | Fucoidan     | Various types: intraductal carcinoma and colorectal adenocarcinoma, mainly | Clinical trial; 92.8% disease control rate in patients with colorectal adenocarcinoma: Letrozole and tamoxifen concentration was not affected by the oral intake of fucoidan extract; Decreased fatigue and increased longevity of patients undergoing chemotherapy | [255-257]                                                                                                                                             |
| Green seaweed      | Kahalalide F | Various types                              | Anti-cancer agent                             | Clinical trial for hepatocellular carcinoma treatment; Induces cell death through oncrosis                                                                                                                         | [6,258,259]                   |
| Brown seaweed      | Algasol T331 | Various types                              | Radioprotective and post-surgical adjuvant   | Increase in physical condition performance, in patients undergoing surgery or radiation therapy (body weight, hematic crasis and erythrocyte sedimentation velocity)                                                | [261]                         |
CONCLUSION

Seaweed consumption can have benefits in the cancer prevention and treatment, yet there is need for more knowledge regarding seaweed nutritional and compounds profiles if to be used as food supplements with health benefits. Otherwise, depending on the dose, seaweed consumption can be a problem to human health.

In cancer therapeutic, there are preliminary studies demonstrating seaweed’s potential against cancer, playing diverse roles in cancer therapy. However, due to the surrounding ecosystem that seaweeds inhabit, there are complex methods to extract and guarantee target compounds’ chemical stability and quality. This way, there is a need to surpass this problem through the production of seaweeds in cultivation systems to guarantee the target quality in all the seaweed biomass produced and which cannot be replicated in the natural habitat, especially with seaweed secondary metabolites.

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