Therapeutic health booster: seaweeds against several maladies

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Seaweeds (marine macro algae) are extremely important oceanic resource having unique secondary metabolites. They have the potential for supporting industrial development as being source of many essential substances such as pharmaceuticals, cosmetics, nutritional supplements etc. Seaweeds offer a wide range of therapeutic possibilities was established only some decades ahead. Several pharmacologically important metabolites have been discovered from seaweeds in recent years, the exploitation of seaweeds for therapeutically active molecules is still in its embryonic stage. In order to harness the rich therapeutic potential of seaweeds the present limited use needs to be diversified into several applications. Present review highlights a state of art on the medicinal value of seaweeds and their exploitation scenario on a global scale.

[Keywords: Bioactive compounds; seaweeds; nutraceuticals; phycocolloids; fucoxanthin]

Introduction
The oceans, which cover 70 percent of the surface of earth, holds 34 out of the 36 phyla of life, whereas, only 17 phyla reside on land1,2. Marine compounds can lead to be the new curative ailments for humanity and thus opening up the possibility of treating many newly evolving drug resistance diseases. Among the diverse variety of marine organisms seaweeds are widely explored for their active metabolites as they can be easily found in shallow areas of the sea and thus are easily assessable as compared to the other marine organisms. There are extraordinary sustainable resources in the marine ecosystem and have been used to satisfy several human needs such as food, feed, fertilizers and medicines since a long time ago.

Seaweeds are commonly classified into three main groups namely phaeophyta, chlorophyta and rhodophyta as per their pigmentation. Pheophyta (brown seaweeds) contains the carotenoid fucoxanthin and the primary polysaccharides alginites, laminarins, fucans and cellulose3-4. Chlorophyta (green seaweeds) are dominated by chlorophyll a and b, with ulvan being the major polysaccharide component5. Rhodophyta (red seaweeds) consist of the principal pigments, phycoerythrin and phycocyanin and the primary polysaccharides agars and carrageenans6.

Marine macro algae possess a great variety of bioactive compounds characterized by a broad spectrum of biological activities. Compounds isolated from marine macro algae have demonstrated various biological activities, such as antibacterial activity, antioxidant potential, anti-inflammatory properties, anti-coagulant activity, anti-viral activity and apoptotic activity7. More than 7000 marine natural products have been isolated, 25% of which are from marine macro algae8. Hence, this data reveals that in the last few decades the discovery of pharmacologically active metabolites from the seaweeds has increased tremendously. The history of Indian seaweed research is not more than 75 years. India has a stretch of about 7500 km coastline9 and the seaweed flora of India is highly diversified and comprise of almost all of the tropical species. The research interest of many academic and corporate institutions to discover new active natural metabolites has initiated many recent studies of seaweeds for several purposes. However, despite this intense research very few marine products are there in the market so far. Several robust new compounds are now in different phases of clinical trials and are in clinical development. Substances that currently receive most attention from pharmaceutical companies for use in drug development or from researchers in the field of medicine-related research include: sulphated polysaccharides as antiviral substances, halogenated

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furanones from *Delisea pulchra* as antifouling compounds and Kahalalide F from a species of *Bryopsis* as a possible treatment of lung cancer, tumors and AIDS. Other substances such as macroalgal lectins, fucoidans, kainoids and alypsiatoxins are routinely used in biomedical research and a multitude of other substances have known biological activities.

Present article focuses on several bioactive chemicals identified in different seaweeds over the last few decades and simultaneously specifies the biological activities for which they are responsible. Health benefits of constituents of edible seaweeds and their role in nutrition and disease prevention has been also highlighted in this review. An attempt has been made to gather sufficient information related to the use of seaweeds in human health care from ancient times till date so as to properly elucidate changes that took place over the years on the subject. Present scenario of the use of seaweed resources for different purposes with major importance to medicinal utility is also discussed.

**Seaweeds as a source of functional foods and nutraceuticals**

Use of some seaweed for human consumption could be traces back to about 300 BC in China and Japan. Even in several other countries like Malaysia, Indonesia, Singapore, Thailand, Korea etc., several seaweeds are widely used as foods. In India however seaweed consumption is negligible, but due to the importance of seaweeds and their derived product as nutraceuticals the seaweed derived food supplements are gaining importance in the market.

There has been an increasing demand for functional food sthroughout the world. Functional foods are foods that produce a beneficial effect in one or more physiological functions increase the welfare and decrease the risk of suffering a particular disease. Recently developed food derived products known as nutraceuticals the seaweed derived food supplements are gaining importance in the market. These are employed as food supplements that can provide important health benefits. It is usually found that this type of functional foods is obtained from traditional foods but they are further enriched with a functional ingredient that can impart some beneficial effect in favor of the human health. Most of the edible seaweeds and their derived bimolecular are widely used as functional ingredient in many functional foods and nutraceuticals for their beneficial effects in countering several maladies. They are excellent source of several important vitamins like A, B, C, D, E, riboflavin, niacin, pantothenic acid, folic acid as well as minerals like I, Ca, P, Na, K etc. Concentration of vitamins like B, B, pantothenic acid and folic acid are usually higher in green and red algae than that of the brown algae. Brown algae however contain iodine in greater amounts as compared to red and green algae. Not only that but also seaweeds are excellent source of most of the amino acids needed for life and health. They are blessed with more than 54 trace elements required for human body’s physiological functions in quantities greatly exceeding vegetables and other land plants. Green seaweeds like *Monostroma*, *Enteromorpha*, *Ulva*, *Caulerpa* and *Codium* are commonly used as source of food. Similarly *Laminaria*, *Undaria*, *Sargassum*, *Cladosiphon*, *Turbinaria* and *Colpomenia* are some of the brown seaweed species that are widely eaten in the form of soup or stew in countries like Japan, Korea, and China etc. Red seaweeds like *Acanthophora*, *Asparagopsis*, *Calophyllis*, *Hypnea* and *Laurencia* are eaten fresh, cooked or used to make jellies.

**Seaweeds against several diseases**

History reveals that prior to 1950s the use of seaweeds for medicinal purpose was mostly restricted to the traditional and folk medicines of some selected maritime countries only. It was in 1980s and 90s, when several pharmacologically active molecules were discovered from various organisms found in the sea. According to available data between 1977–1987 regarding the exploitation of algae for discovering new metabolites, it has been found that they have been the source of about 35% of the newly discovered chemicals, followed by sponges (29%) and cnidarians (22%). Discovery of new products from seaweeds has decreased since 1995 and attention has now shifted to marine micro-organisms. In the last few decades, discovery of pharmacologically active metabolites from the seaweeds has increased tremendously those can be used against several diseases like cancer, diabetes, infectious diseases etc. Although marine compounds are not commonly represented in current pharmacopoeias, it is expected that in the future marine organisms are going to become an important source of novel compounds. Here is a brief review of the agents isolated from the seaweeds effective against several diseases.

**Seaweeds vs. cancer**

In the past three decades, many researchers have worked on the antitumor and anticancer activities of seaweeds. Seaweeds contain large amounts of...
antioxidants and polyphenols which constitute their own protective antioxidative defense systems against cancer cells. Besides, several oligo and polysaccharides derived from different seaweeds have been demonstrated to induce apoptosis in cancer cell lines. Carrageenans (fig. 1) and alginate derived from seaweeds can inhibit the growth of tumors in rodents through immunomodulating activity. According to a study, the alcoholic extract of the red alga *Acanthophora spirifera* exhibits tumoricidal activity on Ehrlich's ascites carcinoma cells developed in mice at a dose of 20 mg/kg, comparable to the standard drug, 5-flurouracil. Likewise an extract from the brown seaweed *Sargassum thunbergii* has shown to inhibit tumor metastasis in the rat mammary adenocarcinoma cell (13762 MAT).

Several sulphated marine macro algal polysaccharides have cytotoxic properties. Fucoidan (fig. 2) moiety obtained from *Ascophyllum nodosum* shows an anti-proliferative effect on both normal and malignant cells, including fibroblasts (Hamster Kidney Fibroblast CCL39), sigmoid colon adenocarcinoma cells (COLO320 DM), and smooth muscle cells. Takara Bio Inc., of Japan produces a range of seaweed based products having promising effect against leukemia, stomach and colon cancer. Active ingredient is a guluronic rich polysaccharide based extract from the kelp *Laminaria japonica*. Active components are fucoidan, laminaran and alginate. Recent literatures revealed that, two derivatives of marine alkaloids namely lophocladine A and lophocladine B, isolated from the red algae *Lophocladia* sp. have anticancer activity.

Several seaweed derived metabolites have proven their efficacy against many forms of cancer. For example, Stylopoldione, isolated from *Stypodium* sp. is a potent cytotoxic metabolite, which halts mitotic spindle formation. Compound Condriamide-A isolated from *Chondria* sp. exhibits cytotoxicity towards human nasopharyngeal and colorectal cancer cells. Caulerpenyne (fig. 3) obtained from *Caulerpa* sp. shows its bioactivity against human cell lines and to have anticancer, antitumor, and antiproliferating properties. Two compounds namely meroterpenes and usneoidone, showing antitumor properties have also been isolated from *Cystophora* sp. As stated earlier, another important metabolite namely Kahalalide F (fig. 4), derived from mollusca, *Elysia rufescens*, is actually produced by the green macro alga *Bryopsis* sp. has shown its efficacy against human prostate, lung and colon cancer. It is currently under phase II clinical trials for the treatment of lung cancer. Similarly another compound namely Apratoxin...
A (fig. 5) obtained from *Lyngbya boulloni* have been found to have cytotoxicity to adenocarcinoma \(^{30}\). Recently reported new metabolite namely Largazole (fig.6) has been isolated from *Symplocaspp.* with antiproliferative activity \(^{31}\). Finally, it may be added here that, owing to a diverse chemical ecology, seaweeds have a great promise for providing potent anticancer agents.

**Seaweeds against obesity and diabetes**

In the present scenario, there is a chase for naturally existing hypolipidemic agents as obesity is a leading cause of death worldwide and it increases the likelihood of various diseases like heart disease, diabetes, obstructive sleep apnea, cancer and osteoarthritis. Also, with increasing prevalence in adults and children, now a day’s it is considered to be a major stigma in much of the modern world. One of the major causes that relates to the increasing prevalence of this condition is the typical modern diet having high amount of refined and processed products and lacking the necessary levels of dietary fiber, minerals and vitamins that are necessary to keep our bodies healthy. Research has shown that incorporation of the right amount of dietary fibers in to ones diet helps in reducing fat absorption. The dietary fiber content of seaweed can be as high as 75% of the total dry weight which comprises the structural polysaccharides *i.e.* alginate and fucoidans (brown seaweeds), carrageenan, agar and porphyran (red seaweeds) and ulvan (green seaweeds). These fibers have been found to produce hypochol esterolemic and hypolipidemic responses as they tend to reduce cholesterol absorption in the gut \(^{32}\). One such product is Polymann\(^{TM}\) (Korea Bio Polymer Co. Ltd), which is based on a purified form of polymannuronic acid from the kelp *Undaria* that helps in controlling blood cholesterol \(^{22}\). In addition to that, seaweeds have low fat content (<2%) and rich source of PUFAs including the essential omega (n)-3s LNA, EPA and DHA and omega-(n)-6 LA (linoleic acid). The n-3 and n-6 fatty acids have opposing physiological functions that require a balance for normal growth and development in humans. A ratio of 5:1 (omega n-6:n-3) is recommended and brown and red seaweeds provide a good balance with such ratios \(^{33}\). It has been also found that the brown algal pigment, fucoxanthin and its metabolite fucoxanthinol have been shown to induce the expression of UCP\(_1\), a protein that suppresses fat accumulation, particularly around internal organs in rats and mice, resulting in an increase of <10% fat oxidation \(^{34}\). Hypolipidemic activities have been identified in ethanolic extracts of *Solieriarobusta*, *Iyengariastellata*, *Colpomeniasinuosa*, *Spatoglossumasperum* and *Caulerparacemosa* in rats \(^{35}\).

Obesity usually causes insulin resistance and which further leads to diabetes. Diabetes is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion or action or both. Among the several types of diabetes type 2 diabetes is of common occurrence and is often associated with the insulin resistance caused due to obesity. Hence, controlled dietary intake and control of blood glucose levels are the two major criteria to control the hyperglycemia in diabetic patients. Some dialectologists suggest that alpha-glucosidase inhibitors are a cost-effective means to prevent the progression of diabetes as this enzyme reduces the absorption of glucose from the gut itself. Seaweeds have shown a unique way in search of natural alpha-glucosidase inhibitors from natural resources. Alpha-glucosidase inhibitory activity and the anti-hyperglycemic effects of a brown alga, *Eckloniastolonifera*, were investigated using non-insulin dependent diabetic mice. Methanolic extract of *E. stolonifera*, which contains a high content of polyphenols, showed strong inhibition of alpha-
Seaweeds, especially the red one, are rich in polyunsaturated fatty acids (PUFAs), mostly eicosapentaenoic and docosahexanoic acids. Oxylipins, metabolized products of PUFAs, found in many red algae almost resemble eicosanoid hormones in higher plants and humans which fulfill a range of physiologically important functions related to inflammation. The *Gracilarialichenoides* have been proven to be rich source of prostaglandins as PGE$_3$ and PGE$_2$. PGE$_2$ and 15-keto-PGE$_2$ were found in *Gracilaria asiatica*. Similarly PGF$_2$ and 15-keto-PGF$_2$ are found in *Gracilaria verrucosa*. Sulphated polysaccharides like fucoidan are well known and marketed for their anti-inflammatory activity. The mechanism is that this moiety promotes the growth of fibroblasts and thus repairs inflamed cells. An eicosanoid like compound named 6-n-tridecysalicicylic acid isolated from the brown seaweed *Caulocytsis cephalornithos* has shown anti-inflammatory activity almost comparable to salicylic acid. A compound named Caulerpeyne, obtained from green seaweed *Caulerpa*, has been shown to be effective against bees stings. High intake of seaweed has been shown to reduce the prevalence of allergic rhinitis, hay fever in Japanese women. These examples and studies suggest that the seaweeds can prove to be better anti-inflammatory agents in the nearby future.

Diverse range of seaweed derived compounds show antimicrobial activity against wide range of microorganisms including bacteria, fungi and also several diseases causing virus. A halogenated furanone, or fimbrolide, that belong to a class of lactones obtained from *Delisea pulchra* has a promising antibacterial activity against chronic *Pseudomonas aeruginosa* infection. Similarlydepsipeptide skahalalide A and F obtained from *Bryopsis* species have activity against *Mycobacterium tuberculosis*. However some studies suggest that sulphated polysaccharides from brown seaweeds, namely fucoidan, are also active against a range of gram positive and gram negative bacteria. Red seaweeds show antiviral activities towards viruses’ responsible for human infectious diseases as they have been proven to be rich source of sulphated polysaccharides. Galactansulphate from *Aghardhiella tenera* and xylomannan sulphate from *Nothogenia fastigiata* are active against human immunodeficiency virus (HIV), Herpes simplex virus (HSV) types 1 and 2 and respiratory syncytial virus (RSV). Some commercial antiviral preparations are readily available. For
example, Carraguard™ (containing 3% carrageenan), which is under phase III clinical trial in South Africa and Botswana in 2003 has been shown to block HIV and other sexually transmitted diseases in vitro. Another sulphated polysaccharide obtained from Schizymeniapacifica inhibits HIV reverse transcriptase.38 Besides, Fucoidan has potent antiviral properties towards viruses such as RSV, HIV, HSV types 1 and 2 and human cytomegalovirus.39 The mechanism involved is that they inhibit binding of the viral particle to the host cell.39 Some uncharacterised polysaccharide fractions obtained from Caulerpa sp., Corallina sp., Hypneacharoides, Padinaa borescens and Sargassum patens have antiviral activity against HSV types 1 and 2 while maintaining low levels of cytotoxicity.40 A product named Viracle™ (Marine BioMedical Research Pty. Ltd., Australia) contains an extract from the kelp Undaria shows confirmed inhibitory activity against HSV and HIV.22 Some seaweeds show antifungal properties. For example, proteins isolated from the red alga Hypneamusiformis were active against human pathogenic yeasts but usually the horticultural industry utilize the antifungal properties of seaweeds more for controlling disease and pest.

Seaweeds as antithrombotic & anticoagulant activity

It has been found that fucoids present in brown seaweeds have in vivo and in vitro heparin-like antithrombic and anticoagulant activities that are mediated by blood coagulation inhibitors such as heparin cofactor II or antithrombin III.41 Further it was also established that this activity usually increases with the amount of sulphation.41 Preparations from the brown seaweeds Acophyll ummodo summand Fucus vesiculosus with sulphated fucanshave been patented as anticoagulants.42 They have also several advantages over heparin. Some older literature suggests that a compound named laminaran (fig.7) have anticoagulant properties but there is every possibility that this activity may be due to fucoidan which is often present in the same extracted fraction as laminaran.42

Seaweeds for beauty enhancement

Recently, seaweeds are becoming increasingly popular for use as Spa and Thalasso therapy products. In the development of Spa products the seaweeds play an important role, whether as seaweed wraps, pastes of milled seaweeds or Iris hot seaweed detox baths.55 Not only this, but also extract of seaweeds is often found on the list of ingredients on cosmetic packages meant for face, hand and body. It has been stated that seaweeds based cosmetics tighten, tone, stimulate blood and lymph circulation, deep clean and increase the moisture levels and elasticity of the skin.56 This may be due to their nutrient and anti-oxidant properties that aid the ability of the skin to absorb and maintain minerals that promote a healthy and glowing appearance and thereby they are now extensively used in cosmetic applications. Several varieties of seaweeds are used in cosmetics at present. Laminaria spp are the most common among the brown algae in cosmetic industry. The bladder wracks such as Fucusvesiculosus and Ascophyllum nodosum are also utilized for different purposes to a limited extent. Similarly among the red algae, Chondrus crispus, Mastocar pusstellatu s and Porphyra spp are widely used as cosmetic ingredients.57 It has been reported that Kelp, brown seaweed containing high amount of silicon, is believed to protect skin from wrinkling and sagging.56 Available information further suggests that many red seaweed derived products like agar and brown seaweed derived product like alginate are commonly used as thickeners in many cosmetics and hair products. Presently several clinical trials have proven the anti-ageing and wrinkle-reducing properties of seaweed derived products. Some of the Australian companies like Maritech and Marinova have reported the clinical usefulness of their seaweed extracts in reducing wrinkles and improving skin appearance of ageing skin.58,59 Thus, seaweeds have proved themselves as miracle in the field of cosmetics.

Demand for seaweeds and seaweed derived Products

Seaweeds became an industrial resource much earlier than any other marine organisms. History supports the fact that the seaweeds have been used as potential source for the production of agar, carrageenan and alginate. Pharmaceutical firms have
The trend of increase during 1996-2004 in seaweed aquaculture production as evident from a report published in the year 1990. It has been projected that the increase could be double through the years. For example, the average production of alginate was increased to 50000 tons by 1995 over the years. For example, the average production of alginate was increased to 50000 tons by 1995 which was between 22000-25000 tons per year as per a report published in the year 1990. It has been projected that the increase could be double through the seaweed aquaculture production as evident from the trend of increase during 1996-2004.

The developed nations of the world are consuming more and more quantities of polysaccharides of all kinds obtained from seaweeds due to their numerous applications, more so in foods and drink preparations, cosmetics, detergents, paints, textiles, automobile products, oil drilling lubricants and many other industrial products. In the U.S.A. alone, some half million tons of seaweed derived polysaccharides of one kind or another are now utilized annually. The recent rates of growth in demand for these products are in order of 8 to 10 percent annually. With such ascending swing of the use of seaweeds the demands can be met at affordable prices shall largely depend upon the availability of raw materials. As the natural resources of seaweeds have been over exploited due to their intensiveuse; the only alternative is to enhance aquaculture production that can supplement the natural stock. The other alternative may be search for new novel compounds from these unique denizens of marine domain. This could be achieved through development in the research programmes concentrated to search new metabolites from seaweeds that can be used to combat the emerging diseases of the present and in future millennium. Hence in the search for “Drugs and pharmaceuticals from the Sea” programme, researchers can concentrate their efforts on the seaweeds to obtain pharmacologically important active metabolites.

Conclusion
The main objective of writing this article is to provide an overview of the medicinal and nutritional properties of seaweeds. As on date the use of seaweeds has shown satisfactory development in several industries especially in pharmaceuticals, cosmetics, nutritional supplements etc. and further expansion is also in good inprogress. However the mystery of exploring new active metabolites from the marine macro algae has not been solved completely. Therefore, it forms an area of research in future. It is hoped that this review will help to spark interest to take forward research work pertaining to the secondary metabolites in seaweeds and their utility. The persuasion of research by researchers to discover the pharmacological significant products and metabolites from seaweeds shall provide tremendous benefit in the new millennium.

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