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Review Article
Discovering Promising Anti-cancer Drug Candidates from Marine Algae

N. Jennifer Michellin Kiruba, M. Andrew Pradeep and A. Joseph Thatheyus

PG Department of Immunology and Microbiology, PG and Research Department of Zoology, The American College, Madurai, India

Abstract

Bioactive secondary metabolites from marine sources are expected to deliver the next line of anti-cancer drugs. Meanwhile, the incidence of cancer across the globe and the number of lives that succumb to it keeps increasing. This review has summed up the efforts taken to screen marine algae (seaweeds) for secondary metabolites that show consistent anti-cancer or anti-proliferative activity in cell line or animal models. Algal sulfated polysaccharides repeatedly showed up in the literature survey in the form of fucoidan, heterofucans and fucoxanthin, suggesting further research requirements.

Key words: Marine algae, seaweeds, anti-cancer drugs, secondary metabolites, polysaccharides

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Corresponding Author: A. Joseph Thatheyus, PG Department of Immunology and Microbiology, PG and Research Department of Zoology, The American College, Madurai, India Tel: 08497424820

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INTRODUCTION

Marine-based drug discovery has been in and out of the limelight in the past few decades. The field is being extensively investigated by many research groups and pharmaceutical companies across the globe. The prominent source of drug elucidation remains numerous species of marine invertebrates and marine invertebrates-associated microbiota. Marine algae are one such source[1].

Gulf of Mannar Marine Biosphere Reserve (GOMBR) is one of the few of its kind and world renowned for its plenteous and multifarious marine diversity. It covers a chain of 21 islands along the South-East coast of India between Rameswaram and Tuticorin with an area of about 10,500 km^2 [2].

It is also often known as "Biologists' paradise"[3], comprising various ecosystems with estuaries, beaches, forests of the near shore environment and six mangrove species endemic to peninsular India. Apart from the seasonally migrating marine mammals, marine fauna and flora include 117 species of corals, 641 species of crustaceans, 731 species of mollusks, 441 species of fin fishes, 147 species of seaweeds.

Along the last few decades, several research institutions have focused on this treasure trove of natural resources. Considerable research has been explored in the fields of ecosystem preservation, biodiversity, finfish fishery, shellfish fishery, aquaculture and seaweed industry in Gulf of Mannar[4]. The Exclusive Economic Zone (EEZ) of Gulf of Mannar covers about 15,000 km^2 in which commercial fishing is carried out in about 5,500 km^2 up to a depth of 50m.

Marine algae: Similar to the fishing industry, the seaweed industry also plays a pivotal part in the economic scenario of the region. More than 60 out of the 700 species of marine algae, are commercially important for the production of agar, algin and carrageenan[5]. Agar, alginate and carrageenan are hydrocolloids, used to thicken (increase the viscosity of) aqueous solutions. Therefore, they are in constant demand from food, cosmetic and pharmaceutical industries. In 2000, the production of total seaweeds in India was approximately 600,000 t (wet weight). India produces 110-132 t of dry agar annually utilizing about 880-1100 t of dry agarophytes. Annual algin production is 360-540 t from 3,600-5,400 t dry alginophytes[6]. The global annual use of seaweeds is about 8 million tonnes of wet seaweeds. Apart from hydrocolloid extraction from seaweeds, their direct consumption as food has also emerged rampantly across the globe. The seaweeds have been used as food since the 4th century and 6th century in Japan and China, respectively. Japan, China and the Republic of Korea are the world's largest consumers of seaweed as food. But, globalization, capitalism and worldwide migration have led several European and American countries to commercialization and promotion of their own seaweed traditions among others. Since seaweed consumption has been linked to the low rate of cancer incidence in the Oriental Asian countries, the amount of research analyzing the bioactive properties of seaweeds was hiked up.

Rising cancer incidence: Due to rising cancer incidence, finding drugs that are cost-effective, effective in long term, immune-enhancing and without side-effects for cancer therapy is the need of the hour. Cancer is not just one disease but many diseases which begins in host cells. There are more than 100 different types of cancers named for the organ they originate from. Cancer is a leading cause of death worldwide, with an estimated 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5 years prevalent cancer cases occurring in the less developed regions[7,8]. The incidence and mortality rates of several cancer types are given in Table 1[9,10].

The total number of cancer patients in India is likely to hike from 979,786 cases in the year 2010 to 1,148,757 cases in 2020. Breast cancer rate alone will cross the figure of 100,000 by 2020 for both genders[9]. Among 14.1 million cases diagnosed in 2012, about 1.67 million cases were that of breast cancer[11]. Relatively, 30% of the breast tumours result from genetic mutations in the breast cancer genes.

Pharmacological properties and clinical efficiency of current drugs are often studied using serum lipid profile of patients under treatment. In a study of cancer patients' population in Madurai, the correlation between serum lipid profiles, reactive nitrogen intermediates (RNI), reactive oxygen species (ROS) and different forms of cancer was analyzed[12-14]. For decreasing breast cancer risk, prophylactic mastectomy is

Table 1: Most common type of cancer, its incidence and mortality rate

Cancer type	Incidence rate in India (ASR per 1,00,000)	Incidence rate worldwide (ASR per 1,00,000)	Mortality rate in India (%)	Mortality rate worldwide (%)
Lip and oral cavity cancer	>6.9	3.2	61	1.0
Lung	4.3-12.1	>41.5	3.9-10.6	34.9
Cervix	20.6-30.2	13.6-20.6	1.4	7.5
Stomach	6.6-9.7	>15.4	1.75	8.8

being widely suggested. But, women often suffer from severe psychological problems, since it affects body image and quality of life adversely, even when combined with reconstruction. A randomized trial of dietary fat reduction showed a 9% decrease in breast cancer risk. Changes in lifestyle, vitamin supplementation in diet, healthy maintenance of physical activity and prevention of obesity are being encouraged for the prevention of breast cancer. Currently various treatments for cancer are available, but most come with die-hard disadvantages, risks, side effects and ethical issues Chemotherapy, radiation therapy, Targeted cancer therapies, transplantations, angiogenesis inhibitors, biological therapy, photodynamic therapy, lasers, hyperthermia, cryosurgery and gene therapy are some of them. The situation requires effective therapeutic strategies to combat the increasing incidence rate with cost-effectiveness. Drugs derived from plant secondary metabolites have shown considerable progress in the treatment and/or prevention of cancer and for cancer chemotherapy[15].

Cancer and algae: In the late 1980's, the antitumor activity of seaweeds came to limelight, leading to a promising future cancer drug development and a spur in research on its mechanisms. A large amount of literatures is available which provides evidence that the seaweeds or seaweed extracts or seaweed-derived components have anti-oxidant and anti-tumor activity. *In vitro* studies are quite often helpful in proving the therapeutic importance of these promising agents. Pilot studies and current research indicate that elucidating metabolites from algae occupies potential in the field of anticancer drug discovery and development.

Lycopene in combination with vitamin E significantly reduced the growth of MCF-7 cell line by 55.83 and 48.3%, respectively[16]. A case-control study among Korean women relating seaweed consumption and breast cancer incidence showed that uptake of *Porphyra* spp. (gim) may decrease the risk of breast cancer[17]. Through a clinical trial among American menopausal women, dietary seaweed was found to explain lower postmenopausal breast cancer (BC) by lowering uPAR[18]. A positive association between the risk of papillary carcinoma in postmenopausal women and seaweed consumption was also identified, by the Japan Public Health Center-based Prospective Study[19]. Concurrent seaweed and soy consumption decreases IGF-1 serum concentrations, associating it with the cases of lower breast cancer incidence in Asian countries[20]. Such examples abound in biological literature. But India, despite being a peninsular subcontinent, is yet to discover the significance of dietary seaweed in its lifestyle.

From 2012-2015, the anti-proliferative, angio-suppressive effect, anticancer, antioxidant, antimicrobial, cytotoxicity activity of *Turbinaria conoides*, *Stoechospermum marginatum* (*C. agardh*), *Enteromorpha antenna*, *Enteromorpha linza*, *Gracilaria corticata* and *Sargassum* sp., have been explored in India[21-25]. The potential antiproliferative activity of seaweeds have been investigated and proved upon several occasions. Fucoidans, sulfated polysaccharides extracted from *Turbinaria conoides* have been shown to inhibit matrix metalloproteases-2 and -9 activities in pancreatic cancer cells[26]. The effect of algal lycopene extracted from *Chlorella marina* in human prostate cancer cell lines showed higher anti-proliferative compared to tomatal-lycopene (TL) -treated groups[27].

Methanolic extracts of saline/brackish water algae, *Enteromorpha intestinalis* and *Rhizoclonium riparium* from Sundarbans, exhibited anti-proliferative activity against HeLa cells through the expression of LC3B-II and consequent occurrence of autophagy[28]. Polar and non-polar solvent extracts of *Caulerpa peltata*, *Padina gymnospora* presented potential antioxidant and antiproliferative activities as well as effects on cell morphology[29]. Swiss albino mice with Ehrlich ascites carcinoma (EAC) treated with ethanolic extract of *Gracilaria edulis* (EEGE) increased the life span of EAC-bearing mice compared with that of the model control mice[30].

Most of the research on bioactive algal compounds is contributed by East Asian countries, Japan, China, Republic of South Korea and Taiwan. The research mostly focuses on drug discovery and development from traditional natural resources. Traditional Chinese medicine (TCM) is an exemplar database which builds a knowledge base about bioactive compounds in traditional herbs[31]. The knowledge is further used to navigate between potential therapeutic candidates for various diseases and disorders though *in silico* screening, *in vitro* and animal model studies. Therefore, it is necessary to look within the locality for cost-effective, commercially viable drug candidates.

The ET-743, aplidin and bryostatin-1 isolated from Mussels and tunicates cultivated in Mediterranean and Black Sea have been found to possess antitumor activity[32]. Carotenoid, fucoxanthin from edible brown algae also acts as sources of antitumor drugs derivatives. The consumption of brown macrophytes is linked to decrease in the risk of cancer development[33]. Polysaccharide extracted from *Sargassum confusum* inhibits sarcomas 180 xenograft in mice, by promoting thymocytes and splenocytes[34]. Acidic sulphated polysaccharides obtained from the seaweed *Ulva rigida* used as an experimental immunostimulant, induced a more than two-fold increase in the expression of several chemokines (chemokine (C motif) ligand 1, chemokine (C-X-C motif)

ligand 12, chemokine (C-C motif) ligand 22 and chemokine (C-X-C motif) ligand 14 (Cxcl14)) and the expression of IL6 signal transducer and IL12 receptor beta-1[35]. Extracts of *Caulerpa prolifera* was found to prevent (AFB(1))-initiated hepatotoxicity in female sprague-dawley rats by promoting significant increase in serum alpha fetoprotein, carcinoembryonic antigen, tumor necrosis factor alpha, nitric oxide, interleukin-1alpha, procollagen III and lipid peroxidation level in the liver. It also induces a significant decrease in food intake, body weight, serum leptin, the activities of glutathione peroxidase, superoxide dismutase and DNA and RNA concentrations in the liver[36].

Metabolites isolated from brown algae such as sulfated polysaccharide of fucoidan and carotenoids of fucoxanthin are found to be potent chemotherapeutic or chemopreventive agents[37]. Other promising therapeutic applications for marine algal compounds also have been explored. A number of fucoidans isolated from edible marine algae have been reported as potential matrix metalloproteinase inhibitors, which can lead to profound applications in nutraceuticals, cosmeceuticals and pharmaceuticals[38].

The presence of bioactive quinones, sterols and isoflavonols, in the crude extracts of *Kappaphycus alvarezii* was found to inhibit microbial growth in a dose-dependent manner[39]. Alcoholic extract of the marine alga *Chlorella vulgaris* was found to exert chemo-preventive effect by modulating the antioxidants status and lipid peroxidation in naphthalene-induced oxidative stress in the albino rats[40]. Zinc oxide (ZnO) nanoparticles synthesised using the extracts of macro-algae *Gracilaria edulis* (GE) was found to induce apoptosis in human PC3 cell lines[41]. Methanol extract of *Gracilaria corticata* (GCME) is reported to produce inhibitory activity against MCF-7 cell line by increasing rate of apoptosis from 18-78%[27]. Fucoxanthin, a marine natural product is regarded for its antioxidant, anti-obesity and anticancer activities and nano-suspension mode of delivery have been suggested to improve efficacy of supplements[42]. *Rhizoclonium riparium* is reported to induce the formation of acidic lysosomal vacuoles in treated HeLa cells and lower the expression of LC3B-II suggesting occurrence of autophagy[43].

The presence of higher amounts of phenols and flavonoids in the extraction of red, brown and green marine algae by chloroform and ethyl acetate produced higher DPPH radical-scavenging and growth inhibitory activities in A549, HCT-15 and PC-3 cells[44]. Polar and non-polar solvent extracts of *Caulerpa peltata*, *Padina gymnospora* presented potential antioxidant and antiproliferative activities as well as effects on cell morphology[45]. Chloroform extract of *C. peltata* and ethyl acetate extract of *P. gymnospora* were reported to have better beta-carotene bleaching inhibitory and total reducing activities relative to the other three extracts (aqueous, methanol, chloroform or ethyl acetate) of the two algae[46].

Treatment of adjuvant-induced arthritic rats with alginic acid extracted from the brown alga *Sargassum wightii* resulted in reduced levels of C-reactive protein, ceruloplasmin and rheumatoid factor along with reduced lipid peroxidation[47]. A sulfated polysaccharide ascophyllan derived from brown algae *Padina tetrastromatica* reduced the activities of anti-inflammatory enzymes, concentration of PGE2 and MPO in carrageenan-induced rats, which is indicative of inflammation and oxidative stress[48]. The ethanol extract of *Gracilariopsis chorda* (GCE) was found to increase cell viability afterhypoxia/reoxygenation (H/R)-induced oxidative stress in cultured hippocampal neurons[49]. Cheung *et al.*[50] have explored several peptides from different marine sources that exhibits antioxidative property. Marine peptide-derived drug (Adcetris®) extracted from sea hare approved by FDA for cancer treatment, is one of the few. De Jesus Raposo *et al.*[51] has compiled numerous polysaccharides isolated from marine sources that have anti-proliferative, tumour suppressor, apoptotic and cytotoxicity activities. Marine macro algal ethyl acetate extracts of *Ulva flexuosa*, *Padina antillarum* and *Padina boergesen* / tested against three cell lines including MCF7, HeLa and Vero was found to cause cell death at 100 μg mL^{-1} [52]. Methanolic extracts at 1000 μg mL^{-1} of *Asparagopsis armata* presented high cytotoxicity rate of 11.22±2.98 against HepG-2 cells[53]. Polysaccharide of *Gp. lemaneiformis* (PGL) has been demonstrated to regulate the expression of 758 genes, which are involved in apoptosis, the cell cycle, nuclear division and cell death in the A549 cell line by transcriptome profiling[54]. Fucoidan, a multifunctional marine polymer, from *Sargassum glaucescens* extracted by a compressional-puffing-hydrothermal extraction process was reported to exhibit antioxidant activities[55]. Some of the secondary metabolites often investigated due to its recurrence among several species of marine algae and consistent anti-cancer, anti-proliferative and cytotoxic activity are provided in Table 2.

The potential anti-proliferative activity of seaweeds has been investigated and proved upon several occasions. Most of the researches on bioactive algal compounds are contributed by East Asian countries Japan, China, Republic of South Korea and Taiwan. The research mostly focuses on drug discovery and development from traditional natural resources. Traditional Chinese medicine (TCM) is an exemplar database which builds a knowledgebase about bioactive compounds in traditional herbs[56]. The Seaweed Metabolite Database (SWMD)

Table 2: Some marine algal compounds that exhibit anti-cancer activity

Metabolite	Marine source	Cancer model
Kappa carrageenan (κ), λ-carrageenan	*Kappaphycus alvarezii*	16-F10 and 4T1 bearing mice
Ulvan	*Ulvalactuca*	Hepatocellular carcinoma, human breast cancer and cervical cancer cell lines
Fucoidan	*Macrocystis pyrifera*	YAC-1 cells
Fucoxanthin	*Undaria pinnatifida*	Human glioblastoma cells
Polysaccharide (PGL)	*Gracilariopsis lemaneiformis*	A549 cell lines
Polyphenols	Marine brown seaweed	Human Panc-3.27 and MiaPaCa-2 cells
Halogenated monoterpenes	*Plocamium cartilagineum*	human lung cancer cells (NCI-H460)
Fucus vesiculosus extract (FVE)	*Fucus vesiculosus*	A549 lung cancer cells
Ascophyllan	*Ascophyllum nodosum*	B16 cells
Stoechospermum marginatum extract (SME)	*Stoechospermum marginatum*	Ehrlich ascites tumor (EAT)
Pheophorbide	*Grateloupia elliptica*	U87MG glioblastoma cells
Polyether triterpenoids	*Laurencia viridis*	Jurkat (human T-cell acute leukemia)
3-Keto-22-epi-28-nor-cathasterone	*Cystoseira myrica*	HEPG-2 (liver) and HCT116 (colon)

provides information about the geographical origin of the seaweed, the extraction method, the known compounds, the chemical descriptors of each compounds and their biological activity as described in the literature. These data enable effective chemo-informatics like QSAR analysis, pharmacophore search, molecular docking and virtual screening for drug discovery[57]. The data pertaining to marine algal metabolites is vast and extensive, but the shortage of literature on volatile organic compounds (VOCs) and other essential oils. There is no dearth of literature on bioactive metabolites and it is essential that the data should be exploited to deliver new drug derivatives and lead candidates. The knowledge is further used to navigate between potential therapeutic candidates for various diseases and disorders through *in silico* screening, *in vitro* and animal model studies.

CONCLUSION

Marine algal derived secondary metabolites are investigated for its recurrent and consistent anti-cancer, anti-proliferative and cytotoxic activity. High-throughput screening of these secondary metabolites should be encouraged for agonist activity. Such large scale screening data can provide anticancer lead drug candidates for synthesis of derivatives and extensive *in vivo* studies. A centralized database for such phytochemical compounds also can be made available so that studies on molecular and genetic basis can be carried out with ease.

SIGNIFICANCE STATEMENT

Marine natural products are a promising arena to look for the next generation of drugs for varying set of diseases. Meanwhile, the incidence of cancer across the globe and the number of lives that succumb to it keeps increasing. Algal sulfated polysaccharides such as fucoidan, heterofucans and fucoxanthin showed promising lead drug candidates against cancer, suggesting further research requirements for researchers. A consensus needs to be reached regarding the different families of drugs that can be derived from marine algae, their mode of action and the probability of providing these phytochemical compounds as dietary supplements for cancer patients.

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