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ALGAE AS SOURCES OF ANTICANCER COMPOUNDS

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ABSTRACT

Algae are one among the dominant species existing in the world. They are present in the form of microalgae and macroalgae. Algae have been used as medicine and food since many centuries. Algae contain many novel bioactive compounds having anti-inflammatory, antimicrobial, and antineoplastic properties. Algae also have special properties to inhibit tumour growth. Since currently available chemotherapeutic drugs are associated with a lot of side effects to patients, researchers are trying to identify newer agents with minimal side effects to cure the disease. This review highlights the anti cancer compounds isolated from algal sources.

Keywords: Microalgae, macroalgae, bioactive compounds, anti cancer

INTRODUCTION

Cancer is one of the life threatening diseases both in the developing and developed countries. Cancer is the second leading cause of the death around the world. According to American Cancer Society, the cancer cases were estimated about 12 million and 7 million death in 2015 and it could be increased to 27 million cases and 17 million death by 2030 **[1]**. It is a group of disease characterized by uncontrolled proliferation of the cells. This is mainly caused by the changes in the lifestyle (unbalanced diet, tobacco smoking), genetic mutations and infectious organism [Human Papilloma virus (HPV), Hepatitis simplex virus (HSV)]. Standard treatments are available to cure the disease such as radiotherapy, chemotherapy and immunotherapy. All these are associated with undesirable side effects to the human

health. These treatments not only affect the targeted tumor growth but also affect the normal cells. Researchers are trying to find out substances having minimal side effects.

In the past, natural resources have been used as medicine for the treatment of many diseases. WHO reported that 80% of the world's population consumed medicine from natural sources in order to avoid side effects **[2,3]**. Most of the anti cancer compounds have been discovered from plant sources and microorganisms. Many naturally occuring chemotherapeutic drugs have been reported such as vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), podophyllotoxin and its derivatives (etoposide, teniposide), camptothecin and its derivatives (topothecan, irinothecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) and others **[4,5]**. Nearly 60% of the drugs approved as anticancer drugs are from natural resources **[6]**.

Algae have been used as both food and traditional medicine in many countries like India, China, Japan, Korea and Ireland **[7]**. Algae consists of several novel biologically active metabolites having biological activities such as anti-viral,**[8]** anti-tumor **[9]** and anti-inflammatory activities **[10]**.

Algae are one of the dominant species existing on earth, which are present in both land and water. They are photosynthetic organisms that convert light energy from the Sun into chemical energy, stored in the form of chemical compounds in the process of photosynthesis. Algae are divided into two groups i) Microalgae (Figure 1) which are unicellular and microscopic in nature and ii) Macroalgae or seaweeds (Figure 2) which are multicellular and larger in nature. Algae act as one of the richest sources of nutrients, vitamins, polysaccharides, fattyacids, aminoacids and several secondary metabolites. Since algae showed the presence of wide array of chemically diverse bioactive compounds, there are chances of discovering new anti cancer therapeutic drugs against the different types of cancers.

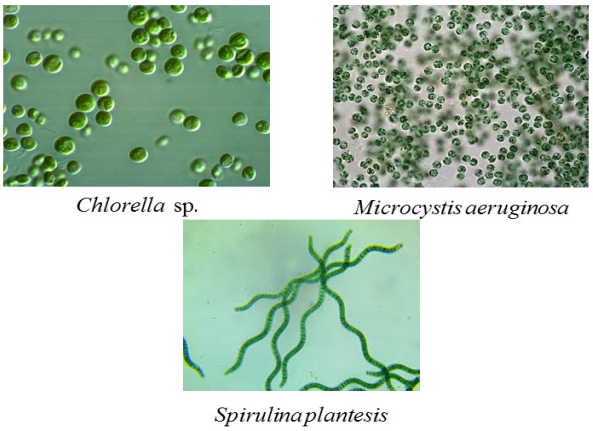

Figure.1: Microalgae

Figure.2: Macroalgae

In this review, anti cancer compounds isolated from different algal species have been discussed.

MICROALGAE AS A SOURCE OF ANTICANCER AGENTS

Microalgae are unicellular organisms existing both in fresh water and marine water. They are present in land, and on trees they exist in the form of lichens. There are about 30,000 known microalgal species. Generally, based on the pigmentation, abundance, nature of photosynthetic storage product and morphological features, the classification of microalgae varies. According to the most frequently used classification, there are Cyanophyceae (blue-green algae), Chlorophyceae (green algae), Bacillariophyceae (including the diatoms) and Chrysophyceae (including golden algae). Among these, blue green algae are present in a wide variety of habitats, larger in number and used in both Industrial production and pharmaceutical applications. Micro algae are major resources of bioactive compounds that act as cytotoxic agents against cancer cells. The compounds from microalgae, such as β-carotene, astaxanthin, the polyunsaturated fatty acids (PUFA) DHA and EPA and the polysaccharide β-glucan have therapeutic significance **[11, 12]**.

Blue green algae are otherwise known as cyanobacteria. Cyanobacteria is the simplest and primitive form and is common to both the bacteria and the algae. The medicinal properties of cyanobacteria were known from 1500BC, but around 1990, cyanobacteria were recognized and used as therapeutic agents. Cyanobacteria such as Microcystis, Anaebaena, Oscillatoria and Nostoc species produce large number of secondary metabolites. Many novel anti cancer compounds have been reported from the cyanobacteria and other classes of algae [Table 1]. Some of the compounds have entered into pre-clinical and clinical studies **[13]**.

Cyanobacteria produce toxins and bioactive compounds such as lipopeptides [40%], amino acids [5.6%], fatty acids [4.2%], macrolides [4.2%] and amides [9%]. Among these Cyanobacterial lipopeptides have cytotoxic [41%], antitumor [13%], antiviral [4%], antibiotic [12%] properties and the remaining 18% include antimalarial, antimycotics, multi-drug resistance reversers, anti feedant, herbicides and immunosuppressive functions **[14]**. The crude extracts of unicellular green algae [*Chlorella vulgaris*) and filamentous blue green algae (*Spirulina plantesis*) were screened for their anti cancer activity on selected cancer cell lines (breast cancer cell line MCF-7 and liver cancer cell line HepG2]. There was 50% reduction in cell viability of treated MCF cells as compared to HepG2 cells. IC_{50} value of *C.vulgaris* was 89 µg/ml which was much higher when compared to that of the ethanol extracts of *Spirulina* and *Chlorella* **[15]**. The extracts of *Chlorella pyrenoidosa* demonstrated chemopreventive activity against human liver neoplasia and carcinogenesis. Microalgae such as *Ankistrodesmus gracilis* VACC-010 and *Amphiprora alta* VACC-077 have exhibited strongest inhibition against KB (human epidermal carcinoma) and HepG2 (human liver cancer) cell lines **[16]**.

Table 1: Anticancer compounds from different algal sources

S.No	Species Name	Compounds	Anticancer activity	References
1	*Haematococcus pluvialis*	Astaxanthin	Breast and Prostate Cancer, Colon, Rectal Cancer	[17,18]
2	*Lyngbya majuscula*	Curacin-A	colon, rectal, C1210 leukemia cells and breast cancer	[19]
3	*Chlorella vulgaris*	Lutein	Colon cancer	[20]
4	*Cyanobium sp.*	Hierridin-B	HT -29 colon adenocarcinoma	[21]
5	*Spirulina platensis*	C-phycocyanin	HeLa cells	[9]
6	*Nostoc sp.*	Cryptophycin - 1	Human tumor cells (Solid tumours)	[22]
7	*Leptolyngbya sp.*	Coibamide -A	NCI H-460 lung cancer and Neuro -2A mouse blastoma cells.	[23]
8	*Sargassum filipendula*	Heterofucan	Cervical cancer cell lines and Hela cells	[24]
9	*i) Fucus vesiculosus* *ii)Cladosiphon okamuranus*	Fucoidan	Lymphoma -Leukaemia, Lung (HS-Sultan cells, HL-60, THP-1 cells, A549 cells) Liver (Huh7 and HepG2 cell line)	[25,26,27] [28]
10	*Laminaria japonica*	Phlorotannins	Hepatocellular carcinoma cells (BEL-7402) and Leukemic cell lines (P388)	[29]
11	*Sargassum vulgare*	Alginates	Sarcoma 180	[30]
12	*Nostoc spongiaeforme var .tenue*	Borophycin	Human carcinoma	[31,32]

DIFFERENT CLASSES OF COMPOUNDS FROM MICROALGAE

Carotenoids

Cartenoid is the major pigment present in the microalgae **[33]** and also in brown seaweeds. Example of carotenoids investigated for their anti tumour activity include β - carotene, Lutein, Zeaxanthin, fucoxanthin and astaxanthin. Cartenoids possess anti oxidant compounds that directly help to reduce the risk of cancer onset. One such study demonstrated that dietary implementation of β - carotene in Azoxymethane (AOM) induced colon carcinogenesis in rats had anti cancer activities against colon cancer **[34]**. Similarly many *in vitro* studies were reported that β - carotene had cytotoxic activities on human colon cancer cell lines **[18]**.

Astaxanthin

Astaxanthin is a xanthophyll carotenoid present in many marine microalgae. The green microalga *Haematococcus pluvialis* is a rich source of astaxanthin which is used for human consumption **[35]**. Maoka *et al*., **[17]** evaluated the anti tumour activity of astaxanthin compound in DMBA/TPA induced skin carcinogenesis mice models. This compound reduced the average number of papillomas per mouse. Similar to this study, the effect of astaxanthin esters from *Haematococcus pluvialis* on UV-DMBA-induced skin cancer in rats were reported. It was found that Astaxanthin esters are more potent to inhibit the proliferation of tumour growth in rats than astaxanthin. The ester had good anti tumour activity which could be due to their increased bioavailability **[36]**. The main role of astaxanthin is to protect the body from UVR rays. UVR radiation is one of the primary causative agents of skin cancer. Astaxanthin rich algal extract provided protection against UVA induced DNA damage to melanocytes, human skin fibroblasts and intestinal CaCo-2 cells. Astaxanthin could inhibit the growth of human Colorectal Cancer cells, including HCT-116, HT-29, LS-174, WiDr and SW-480 **[18]**.

Curacin-A

Curacin -A is the compound containing cyclopropane group thiazoline moiety, isolated from the *Lyngbya majuscula*. This compound possesses anti proliferative activity against colon, rectal, C1210 leukemia cells and breast cancer cells. This also blocks cell cycle progression by inhibiting microtubule polymerization **[19]**.

Lutein

Lutein is a xanthophyll or carotenoid containing pigment and it is isolated from green microalgae. The function of lutein is to protect the cells from ROS damage under stress condition, used as a food

colouring agent and a feed additive in industry **[37]**. It also provides protection to age related macular degeneration in humans **[38].** Lutein from *Chlorella vulgaris* was reported as to have anti cancer property against the human colon cancer cell line (HCT-116) **[20]**. Lutein was known to modulate the proliferative activity of K-ras, protein kinase B (PKB) and β-catenin in DMH induced colon carciongenesis models. **[39]**. Lutein supports to protect the skin from UV rays induced damage. One such study showed that pre-treatment with lutein protected a human keratinocyte cell line (CDD 1102 KERTr) and primary human keratinocytes from foreskins against UVB-induced cell damage **[40]**. Intake of lutein rich food reduced the risk of cancer **[41]**.

Zeaxanthin

Zeaxanthin is a compound isolated from Microalgae. PDGF-induced skin fibroblast migration and PDGFR-β and MAPKs phosphorylation was inhibited in an *in vitro* study by Zeaxanthin, proving its anti-tumour potential **[42].**

Violaxanthin

Violaxanthin is a xanthophyll pigment, isolated from *Dunaliella tertiolecta* [43] and *Chlorella ellipsoidea* **[44]**. Violaxanthin exhibited antiproliferative and pro-apoptotic activity against human cancer cell lines **[43]**.

Fucoxanthin

Fucoxanthin is the xanthophyll containing marine carotenoid present in numerous classes of microalgae (Bacillariophytes, Bolidophytes, Chrysophytes, Silicoflagellates, Pinguiophytes) and brown macroalgae (phaeophytes) **[45]**. Fucoxanthin demonstrated anti cancer activity on many *in vivo* animal models against different types of cancer **[46]**. Several studies indicated that Fucoxanthin had exhibited cytotoxic activity against several human colon cancer cell lines by inducing apoptosis and cell cycle arrest **[47]**. More over the effect of fucoxanthin on cell viability of colon cancer cell lines (Caco-2, HT-29, and DLD-1) was higher when compared to other cartenoids **[48]**.

Hierridin-B

Hierridin - B is a cyanobacterial secondary metabolite and it is isolated from the marine cyanobacteria *Cyanobium sps* (LEGE 06113). When tested on a panel of eight human cancer cell lines, hierridin- B exhibited cytotoxicity against HT -29 colon adenocarcinoma cells **[21]**.

Fatty Acids

During the past decades, lipids from the microalgae were mainly concentrated for the production of biofuel. Recently more research was focused on the Microalgal lipids, due to their pharmaceutical applications in the treatment of

inflammatory pathologies like atherosclerosis, Parkinson's, Alzheimer's, psoriasis or cancer. Poly unsaturated fatty acids (PUFA) provide protection against colorectal cancer. Previously, *in vivo* studies reported that fish oil containing EPA/DHA has potent anti-angiogenic effects especially on colon, breast and prostate cancers through the inhibition of angiogeneic mediators such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), platelet-derived endothelial cell growth factor (PDECGF), COX-2, PGE2, NO, NF-κB, MMPs and β-catenin **[49]**.Recently, PUFA isolated from microalgal oil demonstrated effective chemopreventive properties on AOM -induced colon aberrant crypt foci (ACF) in mice. EPA and DHA not only serve as nutritional supplements but they also provide beneficial effects especially in the resolution of inflammatory processes and thus prevent their progression to cancer **[50]**.

Polysaccharides

Algae are the richest sources of polysaccharides with broad range of biological activities including anti-inflammatory, antioxidant, antiviral, anticoagulant, anticancer and inmunomodulating properties **[51]**.The polysaccharides isolated from several microalgae such as diatoms, chlorophytes, prasinophytes, haptophytes, rhodophytes, dinoflagellates and cyanobacteria were checked on various kinds of cell lines and animal models. GA3P (D-galactan sulfate) is an extracellular polysaccharide, isolated from the marine microalga, Dinoflagellate *Gymnodinium* sp. A (3). GA3P inhibited the growth of several colon cancer cell lines (HCC2998, KM-12, HT-29, WiDr, HCT-15 and HCT-116) and also inhibited DNA topo I and topo II isomerases **[52]**.

Proteins

Several therapeutic bioactivities such as hepatoprotective, anti-inflammatory, immunomodulating, antioxidant and anticancer have been reported from algal proteins especially phycobiliprotein from cyanobacteria (*Spirulina platensis)* and red algae (*Porphyridium)* **[53,54].**

C-phycocyanin

Phycocyanins are water soluble, non toxic in nature having anti cancer, anti oxidant and anti viral properties. Phycocyanins contain phycobiliprotein in the cyanobacteria and secondary phycobiliprotein in the red algae. Phycocyanins are given as nutrient supplements for cancer patients who are undergoing chemotherapy. Phycocyanin is one of the promising compound which is significant in therapeutic uses **[55,56]**.The phycobiliprotein, C-phycocyanin, isolated from *Spirulina platensis* caused the release

of cytochome C from mitochondria and caspase-dependent induction of apoptosis in HeLa cells **[9]**. C-phycocyanin mediated mitochondrial-dependent apoptosis in the DMH-induced rat model of colon carcinogenesis **[55]**.

Phycocyanins were well studied in the cyanobacteria, *Spirulina plantesis*. The mechanism is inhibition of cell growth by apoptosis and stimulation of the expression of proto- oncogene, c-myc **[9]**. Phycocyanin from *A.agricanum* when tested *in vivo* on the myeloid graffi tumours in hamsters, resulted in decrease of tumour transplantability and delayed the development of graffi tumour and improved the survivial of tumour bearing hamsters **[57]**.

Peptides

Peptides from microalgae also have anticancer activities. For example, Cyanobacterial peptides such as Symplocamide A from *Symploca* sp.**[58]**, Somocystinamide A from *Lyngbya majuscule* **[59],** Apratoxin D from *Lyngbya majuscula* and *Lyngbya sordida* **[60]**, Dragonamides C and D from *Lyngbya polychroa* **[61]** and Mitsoamide from *Geitlerinema* sp. **[62]** demonstrated anti cancer activities.

Cryptophycin

Cryptophycin is a cytotoxic depsipeptides isolated from Nostoc sp **[63]**. In 1990, Cryptophycin were first reported as anti fungal agents against filamenteous fungi and yeasts **[64].** The main mechanism of cryptophycin is to inhibit microtubule assembly that leads to cell cycle arrest in the G2/M phase. Cryptophycin 52 which is an analog of cryptophycin 1, entered into phase II clinical trial and found to be an effective drug against platinium -resistant ovarian cancer **[22].**

Apratoxin

Apratoxin is a cyclic lipopeptide possessing anti tumour activity, isolated from *Lyngbya boulloni* [65]and *L.majuscula*. This peptide exhibited cytotoxicity against human cancer cells *in-vitro* and *in-vivo* in which mice were able to recover from the early stages of adenocarcinoma. In another study, it was tested against 60 human cancer cell lines and found to exhibit cytotoxicity against cancer cell lines by inducing apotosis **[66]**.

Stypoldione

Stypoldione is a cytotoxic metabolite isolated from *Stypopodium zonale*, was reported to inhibit microtubule polymerization and to prevent mitotic spindle formation **[23]**.

Desmethoxymajusculamide C (DMMC)

Anti tumour activity against human colon cancer cell lines HCT-116 was confirmed in an *in vitro* study from a cyclic depsipeptide known as

Desmethoxymajusculamide C (DMMC), isolated from the cyanobacterium *Lyngbya majuscula.*

Symplostatin

The Antitumour effect of Symplostatin against murine solid tumor model, murine colon adenocarcinoma 38, and in C57B1/6 mice was analysed and confirmed. Symplostatin was isolated from the marine cyanobacterium *Symploca hydnoides* **[67]**.

Borophycin

Borophycin is a polyketide compound isolated from *Nostoc linckia* and *Nostoc spongiarforme vartenue* reported to have anti tumour activity against LoVo and KB cell lines **[31,32]**.

Grassypeptolide A(77) and **C(79)**

These compounds were isolated from *Lyngbya confervoides,* and they possess anti proliferative activity against Hela and HT 29 cells and were also found to arrest the cell cycle at G2/M stage **[68]**.

Coibamide-A

Coibamide-A is a potent anti -proliferative depsipeptide isolated from a marine cyanobacteria *Leptolyngbya* sps. It exhibited cytotoxicity against NCI H-460 lung cancer and Neuro -2A mouse blastoma cells **[23]**.

Dolastatin

Dolastatins are microtubule-disrupting agents produced by *Lyngbya* sp. *and Symploca* sp. Dolastatin analogs such as Pitipeptolides, Symplostatin exhibited anti tumour activity against colon cancer cell lines **[69]**. They demonstrated cytotoxic activity on a panel of human ovarian and colon carcinoma cell lines which was more stronger than paclitaxel or vinblastine **[70]**. Soblidotin (synthetic anolog of dolastain -I) which entered into phase II clinical trials, had exhibited cytotoxicity against human colon adenocarcinoma **[71]**.

Calothrixins

Calothrixins are quinone-based natural products isolated from the cyanobacteria *Calothrix,* which show potent antiproliferative properties against several cancer cell lines **[72]**. Calothrixin B displayed antiproliferative activity against HCT-116 colon cancer cell line (IC50 of 0.32 μM) **[73]**. Malyngamides are small amides produced by marine cyanobacteria *Lyngbya majuscule* (malyngamide C and 8-epi-malyngamide C) found to be cytotoxic to HT29 colon cancer cells (IC_{50} 5.2 μM and 15.4 μM, respectively) **[69]**.

MACROALGAE AS A SOURCE OF ANTI CANCER AGENTS

Macroalgae are large multi cellular organisms present in both fresh water and marine water. Macroalgae present in fresh water are in the form of filamentous algae (eg. Spirogyra). Marine macroalgae are also known as seaweeds. They do not have stem, root and leaves. Seaweeds are

broadly classified into three types i) Phaephyceae/Brown algae - eg., *Laminaria, Fucus, Sargassum* ii) Rhodophyceae/Red algae - eg., *Gelidium, Palmaria, Porphyra* iii) Chlorophyceae/Brown algae - eg., *Ulva, Codium* **[74]**. According to FAO, seaweed industries provide excellent resources all over the world **[75]**. Seaweeds are mainly used as nutritional supplements in the form of foods and also for the production of hydrocolloids. Macro algae derived compounds have a wide range of biological activities such as antibiotic, antiviral, antineoplastic, antifouling, anti-inflammatory, cytotoxic and antimitotic **[76]**.

In the past decades, pharmaceutical industries are targeting on marine resources for developing therapeutic drugs. Some of the compounds isolated from marine resources like sponges and microorganisms have been currently approved as drugs. The terpenoids are a class of compounds isolated from the algae in the year 1970-1980s. Chemical investigation of these compounds have led to the identification of other classes of compounds derived from brominated, nitrogen, oxygen heterocycles, phenazine derivatives, sterols, aminoacids, amines and guanidine derivatives **[8,77,78]**. Since ocean has covered more than 70% of earth's surface and millions of species are available which include both microalgae and macro algae **[79]**, researchers are interested to isolate and identify compounds from the algae in order to develop a therapeutic drug, thereby to prevent the chronic diseases including cancer.

Seaweeds are rich in minerals, vitamins, fatty acids, aminoacids, fibres and bioactive metabolites such as phlorotannins, alginates, sulphated polysaccharides and cartenoids **[80,81,82,83]**. Moreover, some studies reported that seaweed consumption has limited side effects when carried out on chronic animal/short term clinical studies. For human clinical trials, safety tests need to be carried out for using seaweeds as anticancer agents.

Paul and Kundu **[84]** reported that methanolic extract obtained from the green alga *Enteromorpho intestinalis* and *Rhizoclonium riparium,* exhibit anti proliferative potential against cervical cancer cell line Hela with IC_{50} values 309.048±3.083 µg/ml and 506.081±0.714 µg/ml respectively. Patra and Muthumaran **[85]** evaluated *in-vitro* and *in-vivo* studies of the anti tumour activity of the ethanolic extract of *Gracilaria edulis* (Brown algae) on the Ehrlich Ascites Tumour cells. *In-vitro* studies indicated that the extracts were cytotoxic to EAT cells which was mediated through their ability to produce reactive oxygen species (ROS). *In - vivo* studies by

administration of the ethanol extracts intraperitoneally to the EAT induced mice demonstrated antitumour activity and the life span of the mice increased significantly. In the year 2012, Sunderasan and Subbaiah **[86]** investigated the antitumor activity of the methanol extract of *Chondrococcus hornemanni* and *Spyridia fusiformis* against Dalton's lymphoma ascites (DLA) tumour. The methanol extract of algal biomass given orally to mice (200 mg/kg/day) for 14 days caused significant reduction in body weight, packed cell volume and viable tumour cell count when compared to the mice of the DLA control group. Yeh *et al*., **[87]** reported that methanolic extract of red algae *Gracilaria tenuistipitata* showed effective cytotoxic activity against Ca 9-12 (oral cancer cell line) which was mediated through increased ROS generation, GSH depletion, caspase activation, and subsequent cell death. The IC_{50} value of MTS based cell viability assay was 326 µg/ml.

Carageenan

Carageenan is a sulphated polysaccharide and a potent anti viral inhibitor. It contains d -galactose and 3,6 anhydro-d-galactose. It was extracted from rhodophyceae and was used as food from many centuries. Recently, carageenan exhibited therapeutic values against HPV **[88]**.

Fucoidan

Fucoidan is a sulphated polysaccharide which is isolated from brown alga, such as *Laminaria* and *Fucus*. It contains fucose units and sulfate ester groups and also contains galactose, mannose, xylose, glucose and glucuronic acid **[89]**. Fucoidan acts as a dietary supplement and has medicinal properties. Fucoidan demonstrated growth inhibitory effects through the induction of cell cycle arrest, induction of apotosis, modulation of growth signaling molecules and anti -angiogeneic activities. A recent study showed that fucoidan could potentiate the anti cancer activity of established chemopreventive agents such as cisplastin, tamoxifen, paclitaxel against breast cancer **[90]**. Fucoidan from *Fucus vesicuosis* inhibited the growth of HCT-15 cells (human colon carcinoma) by apoptotic events. Moreover, low-molecular weight fucoidan isolated from *Ascophyllum nodosum* had anti-proliferative effects on both normal and malignant cells, including fibroblasts (Hamster Kidney Fibroblast CCL39), sigmoid colon adenocarcinoma cells (COLO320 DM), and smooth muscle cells. Fucoidan exhibited antitumor, anticancer, antimetastatic, and fibrinolytic properties in mice **[25]**.

Heterofucan SF-1.5V is a sulphated polysaccharides rich in L-fucose isolated

from *Sargassum filipendula,* which exhibited anti cancer activities on cervical cancer cell line Hela. It was found to be very effective in inducing cell death as this drug releases mitochondrial apoptosis inducing factor (APaf) into cytosol and at the same time decreases anti apototic factor, Bcl-2 and increases the level of apoptosis inducing factor, Bax **[24]**.

Fucoxanthin

Fucoxanthin isolated from *Sargassum siliquastrum* reduced UVB-induced intracellular ROS production, cell damage and apoptosis in human fibroblasts in a dose-dependent manner **[91]**. In a similar way, this compound attenuated the levels of ROS in H_2O_2-treated HaCaT keratinocytes as well as quenched the hydroxyl radical generated by the Fenton reaction in a cell-free system. Using 7,12-Dimethylbenz[a]anthracene (DMBA) as an initiator and 12-*O*-Tetradecanoylphorbol-13-acetate (TPA) as a promoter, anti tumoural activity of synthetic glycoglycerolipids was evaluated in an *in vivo* two stage mouse skin carcinogenesis model by Colombo *et al*., **[92]**. The results showed that the formation of papillomas were delayed, as well as number of the papillomas per mouse were also reduced. Anti-tumour promoting effects of other synthetic glycoglycerolipid analogues on mouse skin on the same model was confirmed by these authors.

Sulfated polysaccharide

Selective and dose dependent suppression of proliferation of cancer cell lines *in-vitro* was confirmed from sulphated polysaccharide which was purified from the brown alga *Eclonia cava.* The polysaccharide is composed of fucose (82%), galactose (14%), and small amounts of xylose and mannose. Its high anticoagulant activity was investigated for its antiproliferative effect on murine colon carcinoma (CT-26), human leukemic monocyte lymphoma (U-937), human promyelocytic leukemia (HL-60), and mouse melanoma (B-16) cell lines. The growth inhibition rate of CT-26 cells increased consistently with the sample concentration, in which the highest activity (around 40%) was recorded at 100 µg/mL of sample. The compound dose dependently enhanced DNA fragmentation on U-937 cell line **[93]**.

Phlorotannin

Phlorotannin was isolated from brown alga *Ecklonia* sp. It consists of several units of phloroglucinol linked with each other and it was found to inhibit hyaluronidase enzyme involved in allergic reactions, migration of cancer, and inflammation **[94]**.

CONCLUSION

From this ongoing review, it can be concluded that algae contain a wide variety of secondary metabolites which have demonstrated significant biological activities. Researchers have reported many anticancer compounds from algal sources. But there are only limited clinical trials being carried out on algal bioactive compounds. Since algae exist as dominant species on the earth and varieties of compounds being present in each and every species, there is great potential among the algae to identify novel anticancer agents.

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