

Algae as potential repository of anti cancerous natural compounds

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Abstract

Algae constitute a promising source of novel compounds with potential as human therapeutic agents. In particular, algae have been considered as a potential source of new bio-active compound. Algae possess several biological activities, including anticancer activity. This review provides a comprehensive report on the several genera of algae belonging to Chlorophyceae, Pheophyceae and Rhodophyceae having anti-proliferative, apoptotic, anti angiogenic as well as cytotoxic efficacy and their mode of action *in vitro* as well as *in vivo* condition. Algae are extensively used as functional foods and medicinal herbs, and have a long history of use in Asian countries. Many algae have been used for the treatment of cancer, many crude or partially purified polysaccharides from various brown, green, and red algae have been tested for their antitumor activities. Relevant information was collected from scientific journals, books, and reports via library and electronic search using Medline, Pub med, Science Direct, and Scopus. The different extracts with some other solvent shows a huge anti-proliferative action on different cancer as well as on different leukemia cell lines. Here we focus on several bioactive compounds that have been derived as well as characterized from different genera of algae and there mechanism of inhibiting cancer cell growth. Considering the ability of the golden treasure present in algae to act against different cancers, this review highlights the potential use of algae as anticancer agents.

Keywords: Algae; Bioactive compounds; Anti cancer agents

Introduction

Cancer is a serious problem constituting the second most life threatening disease after cardiac complications [1] featured by the uncontrolled cell proliferation and its propagation [2]. Statistical report of GLOBOCAN proclaimed that 14.1 million new cancer cases evolved, within which 8.2 million cancer deaths eventuated in 2012 worldwide. Though cancer is a social burden both in financially developed and developing countries and the incidence rate is twice in developed country than the developing countries, the survival rate is greater in developed nations than that of less developed nations [3]. More than 200 types of cancers are predominant worldwide and some of these are gender specific [3]. Lung cancer and breast cancer are most frequent types of cancer diagnosed in male and female respectively, both in developed and developing countries [3]. Smoking, high alcohol consumption, obesity, least exercise, low anti-oxidant diet, are the most likely external factors [4] and genetic or epigenetic mutations, dormancy of tumor suppressor genes, hyper-expression of oncogenes, deregulation of intracellular signaling cascades, degeneration of apoptosis are the leading internal factors that instigate the mainspring of cancer [5]. Although numerous chemotherapeutic

drugs have been unmasked, the limited access and health systems may be the probable reason for the increasing rate of mortality due to cancer in less developed countries [6]. Plants have been used to prevent and treat diseases since the dawn of civilization on earth. For thousands of years, medicinal plants have been the part and parcel for humankind for their pain-relieving capabilities and healing abilities. Besides several angiospermic plant products, thallophytes like algal components are being used recently as different cancer blocking pathways [7]. Algal extracts have shown to induce apoptosis in different types of cancer cells. There is a good amount of literature recently pouring in which focuses on the isolation of bio active compounds from algae having anti cancer potential. This review focuses on the different algal species having potential bioactive natural compounds that exhibit not only anti-oxidant, anti-inflammatory effects but also anti-carcinogenic activity.

Algae and cancer

Several genera of the algal group particularly Chlorophyceae, Pheophyceae and Rhodophyceae exhibit very efficient cytotoxicity, apoptotic, anti-proliferative and anti-angiogenic effects on different cancer as well as leukemic cells. Various algal alcoholic extracts,

water extracts, polysaccharides and algae derived compounds are engaged in onset of several apoptotic pathways, increase in mitochondrial membrane potentiality, up regulate the reactive oxygen species (ROS) of these cancerous cells *in vitro* as well as *in vivo* conditions. Therefore our mission of this review is to understand the engagement of bioactive components isolated from different algal sources and their interactions with immortal cellular activities.

Anti cancer compounds from Green algae

Green algae or Chlorophyceae grow in fresh water as well as marine. The prevalent pigments of green algae are chlorophyll a, chlorophyll b, beta carotene and xanthophylls. Different genus of this group exhibit huge bioactive properties, some of which are mentioned below:

Capsosiphon

Capsosiphon fulvescens is a well known green marine alga that is used as sea-food as well as potential anticancer drug. Cf glycoprotein (Cf GP) exhibits antitumor activity towards several cancer cells via inducing different pathways. Cancer cells exhibit up regulation of Wnt signaling pathway. Wnt 1 acts through canonical pathway. Analysis of Frizzled receptor, Wnt 1 signaling proteins Axin, LRP, β catenin, APC and GSK-3 beta reports the suppression of Wnt 1 signaling, β catenin and transcription factors in AGS cells through Cf-GP. Western blotting and RT-PCR related experiment of transcription factor Tcf/LEF also proved the decrease level of Wnt-1 signaling pathway and arrests the G0/G1 phase of AGS cells via Cf-GP [8]. Several dose dependently pro apoptotic inhibition can be observed in human gastric cancer cells (AGS cells) by MTS assay and western blot. Caspase-cascade and PARP, a substrate of caspase-3 and -8, and proteins of the Bcl-2 family, are activated by Cf-GP. Cf-GP treatment stimulated not only the release of cytochrome C and apoptotic protease activating factor-1 from mitochondria to the cytosol but also inhibited the growth of AGS cells through induction of sub-G1 phase arrest which decrease in the expression of cyclin D, cyclin E, Cdk2, Cdk4, and Cdk6, and an increase in the protein levels of p21 and p27 [9] (Table 1).

Chlorella

Chlorella is one of the important genera among green algae. Lycopene (Figure.1a) a component isolated from green algae *Chlorella marina* has been reported to exhibit potential anti-proliferative and apoptotic effect on prostate cancer cell line. Exposure of PC-3 and DU-145 cell lines to algal lycopene (AL) at a dose of 20 and 50 μ M significantly down regulate the growth and colony formation, and the percentage of inhibition was higher than total lycopene (TL)-treated groups. Stronger apoptosis signal was

induced with higher concentrations (50 μ M) of algal lycopene. Increased DNA damage was observed in AL- and TL-treated cells which appear in the comet assay. Flow cytometry results indicate that AL treatment caused PC-3 cells to accumulate in the G₀/G₁ phase and to undergo apoptosis. The effect was higher in AL groups than TL-treated groups (Table 1). Algal lycopene showed very significant anti-proliferative and apoptotic effect in human prostate cancer cell lines. Therefore, algal lycopene from *C. marina* would be recommended for the treatment of prostate cancer [10]. Now a day, Chlorella is also been used as nutritional supplements in healthy human as well as in patient.

Cladophoropsis

The marine green alga *Cladophoropsis vaucheriaeformis* have been reported to exhibit cytotoxicity against L1210 cells (Table 1) at 50-100 μ g/ml conc. The cytotoxicity was best at a conc. of 50 μ g/ml and also indicate antitumor substance with additional effect against mouse leukemia [11].

Codium

Spectroscopic analysis reveals that sterol component 24-R-stigmasta-4,25-diene-3 β ,6 β -diol, along with three known compounds, isolated from the green alga *Codium divaricatum* was used as a traditional Chinese medicine, which is efficacious also against cancer [12].

Dunaliella

Dunaliella are unicellular, elliptical, free moving, marine green algae under Chlorophyceae. Fucoxanthin, Neoxanthin and Violaxanthin (Figure. 1c-d) are three bioactive compounds isolated from *Dunaliella* by chromatography, shows some anti proliferative activity. The dichloromethane and ethanol extract exhibits anti proliferation against *in-vitro* cancer cell line like MCF-7 breast cancer cells (Table 1), MDA-MB-231, A549 and Prostate cancer cells i.e. LNCaP [13].

Enteromorpha

Enteromorpha is one of the important genus under Chlorophyceae. Beside showing antimicrobial and antioxidant activity, it also significantly exhibits some anti proliferative nature. The IC₅₀ values of DPPH scavenging activity and superoxide anion radical scavenging activity using acetone extract of *Enteromorpha sp* shows moderate activity 732.12 \pm 2.93 μ g/ml and 913.52 \pm 2.73 μ g/ml respectively. The same extract treatment on Fem-x, A549, LS174 and K562 cell line (Table 1) shows growth inhibitory effects resulting the IC₅₀ values 74.73 \pm 0.58, 155.39 \pm 2.36, 114.48 \pm 1.37 and 82.24 \pm 1.09 respectively [14]. Another report reveals that

methanolic extracts of *Enteromorpha antenna* and *Enteromorpha linza* possesses greater phenolic content (1.816 ± 0.05 GAE mg/g) and (0.912 ± 0.032 GAE mg/g) are the best resources of antioxidant compounds and also possesses ant cancer activity[15]. A potent compound pheophytin, derived from *Enteromorpha prolifera* might be partially associated with the in vivo anticarcinogenic activity [16].

Helimenda

Different dilution extracts of *Helimenda tuna* shows cytotoxic effects on MCF-7 (Table 1) breast cancer cell line [17].

Udocea

Dichloromethane: Methanol extracts of cultured *Udotea flabellum* shows some anti proliferative activity against laryng cervix He La,

cervix squamous SiHa (Table 1) compared with the noncultured ones [18].

Ulva

Ulva fasciata, also known as sea lettuce, an edible alga under the class Chlorophyceae, Family Ulvaceae, is commonly found in high nutrient zone. The extracts of *Ulva* were tested on HCT 116 human colon cancer and it shows an outstanding effect. It inhibited HCT 116 human colon cancer cells by 50% at a concentration of 200 μ g/ml. Some apoptotic change has been found like formation of apoptotic body, DNA fragmentation, an increase in the population of apoptotic sub-G0/G1phase cells, and mitochondrial membrane depolarization. Concomitant activation of the mitochondria-dependent apoptotic pathway occurred via modulation of Bax and Bcl-2 expression (Table 1), resulting in disruption of the mitochondrial membrane potential and activation of caspase-9 and caspase-3 [19].

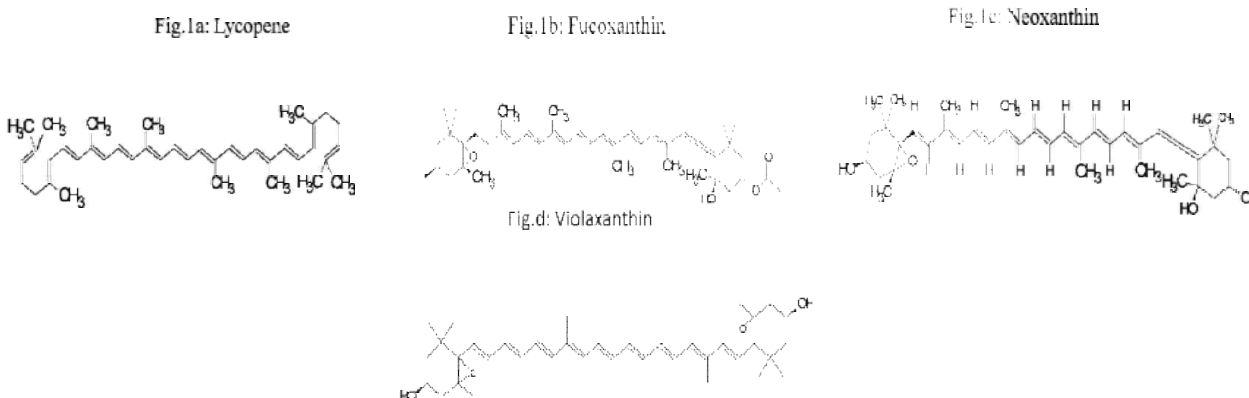


Figure. 1: Structure of anti cancer compounds derived from Green algae.

Table 1: List of Green algal species acting on different cancer cell types.

Name of the algae	Cell types	References
<i>Capsosiphon fulvescens</i>	AGS cells	[8, 9]
<i>Chlorella sp</i>	PC-3 and DU-145	[10]
<i>Cladophoropsis vaucheriaeformis</i>	L1210 leukemia cells & normal NIH-3T3 cells	[11]
<i>Codium divaricatum</i>	--	[12]
<i>Dunaliella sp</i>	MCF-7, MDA-MB-231, A549, LNCaP	[13]
<i>Enteromorpha antenna, Enteromorpha linza</i>	A549, LS174, K562	[14, 15, 16]
<i>Halimenda discoidea</i>	MCF-7 breast cancer cell line	[17]
<i>Udotea flabellum</i>	HeLa, SiHa	[18]
<i>Ulva sp.</i>	HCT 116	[19]

Anti cancer compounds from Red algae

Red algae or Rhodophyceae are mainly marine in nature. The main pigments present in it are phycoerythrin and phycocyanin; beside these two, the other pigments, Chlorophyll

a (no Chlorophyll b), beta-carotene and a number of unique xanthophylls. Many of these contain some antiproliferative activity that are discussed below:

Callophycus

Callophycin A (Figure. 2 a) a marine natural product displaying a tetrahydro- β -carboline scaffold was isolated from a red algae *Callophycus oppositifolius* which exhibits anticancer and cytotoxic activity. Different structural analogues of callophycin A have been formulated for production of a chemical library and have been tested on MCF 7 cell line (Table 2). Results indicate that the *S* isomer of callophycin A showed the most potent anti proliferative activity on MCF 7 cell line [20]. Another research group showed pharmacological activities of four compounds named as bromophycolides R–U (1–4) isolated from another species *Callophycus serratus*, tested on 12 different cancerous cell lines like breast (BT-549, DU4475, MDAM-468, and MDA-MB-231), colon (HCT-116), lung (SHP-77 and A549), prostate (PC-3, LNCaP-FGC, and DU145), ovarian (A2780/ DDP-S), and leukemia (CCRF-CEM) cancer cell lines (Table 2), [21].

Galaxaura

Galaxaura is a thaloid red algae mostly found in ocean. It is widely distributed in Pacific and Indian Ocean. A compound naming galaxamide (Figure. 2b), a cyclo-pentapeptide isolated from *Galaxaura filamentosa* showed some incredible *in vitro* anti proliferation against hepatic cell line (HepG2) and renal carcinoma cell line (GRC-1) [22]. Different skeletal modifications were performed for better activity. MTT assay shows that modified structure of the cyclo-pentapeptide with an analogous named as A5 remarkably increase in the cytotoxicity and also lowers the IC₅₀ values than original compound as well as analogues. Western blot and flow Cytometry data reveals that galaxamide or A5 compound flourish apoptosis at 72 hours than early apoptosis through caspase dependent mitochondria mediated activity in HepG2 cell [23]. Ethyl acetate extracts of *Galaxaura* significantly down regulates HuH-7 cells and leukemia U937 and HL-60 cells (Table 2) in dose and time dependent fashion. Also antioxidant N-acetylcysteine effectively blocked Go-EA-induced apoptosis, which indicates ROS is a key mediator in the apoptotic signaling pathway [24]

Gelideilla

This is red algae commonly known as seaweed moss. Chloroform, ethyl acetate, and aqueous extracts of *Gelidiella acerosa* were reported so far for their anti cancer activity. The result shows greater extraction of phenols and flavonoids by chloroform and ethyl acetate, which exhibit much higher activity in different biochemical assays. These non-polar Chloroform and Ethyl acetate extracts showed higher DPPH radical-scavenging and growth inhibition in Lung cancer (A549), Human colon Cancer (HCT-15), and Prostate cancer (PC-3) cell lines. Higher ferrous ion chelation (aqueous extracts) and growth inhibition in MG-63 cells by methanol and aqueous extracts have been reported [25].

Gelidium

An agar cultivated red algae *Gelidium amansii* shows some incredible results on different cancerous cell lines murine hepatoma (Hepa-1) and human leukemia (HL-60) cells, as well as a normal cell line, murine embryo fibroblast cells (NIH-3T3) (Table 2). *G. amansii*, both in phosphate-buffered saline (PBS) and methanol extracts from dried algae as well as the dimethyl sulfoxide (DMSO) extract from freeze-dried *G. amansii* agar, down regulated Hepa-1 and NIH-3T3 cell growth, but not the growth of HL-60 cells. Annexin V-positive cells were seen in methanol and DMSO extract-treated, but not PBS extract-treated Hepa-1 and NIH-3T3 cells, suggesting that the lipid-soluble extracts of *G. amansii* induced apoptosis [26].

Gracilaria

A group of scientist showed the anti proliferative and apoptotic effects of *Gracilaria edulis*. They showed Ethanol Extract of *Gracilaria edulis* (EEGE) induce apoptosis by the mechanism of Annexin-V positive cells, increased levels of DNA fragmentation and increased caspase-2, caspase-3 and caspase-9 activities. Intra peritoneally administration of EEGE to EAT-bearing mice helped to increase the total lifespan of the animals significantly inhibited tumor growth and increased survival of mice [27]. Another group published that methanol extract of *Gracilaria tenuistipitata* and edible sea weed, had apoptosis-based cytotoxicity against oral cancer cells through the DNA damage, ROS induction, and mitochondrial depolarization, which significantly reduced the oral squamous cell carcinoma (OSCC) [28]. Ethanolic extract of GE increased the life span of EAC-bearing mice compared with that of the model control mice in dose dependent fashion. One group showed that metallic silver (Ag) and zinc oxide (ZnO) nanoparticles using the extracts of macro-algae *Gracilaria edulis* (GE) exhibits its anticancer activity against human prostate cancer cell lines (PC3) (Table 2) [29].

Laurencia

Genus *Laurencia* is found globally on shores in temperate to tropical area, "littoral to sublittoral," and are seen at depths up to 65 m deep. Several extracts of *Laurencia papillosa* [30], *Laurencia similis* (Ceramiales) [31] shows anti proliferative activity in different cancers. Elatol, a compound (Figure. 2 c) isolated from *Laurencia microcladia*, down regulate the cyclin-D1, cyclin-E, cyclin-dependent kinase (Cdk) 2 and cdk4. Elatol has been reported to decrease the expression of bcl-xl and an increase in bak, caspase-9 and p53 expression resulting in activation of the apoptotic process in *in vivo* condition in C57Bl6 mice [32]. Isoaplysin (Figure. 2d) and debromoaplysinol (Figure. 2e) two compounds isolated from *Laurencia pacifica* showed huge inhibition against a panel cancer-derived cell lines of colon (HT29), glioblastoma (U87, SJ-G2), breast (MCF-7), ovarian (A2780), lung

(H460), skin (A431), prostate (Du145), neuroblastoma (BE2-C), pancreas (MIA), murine glioblastoma (SMA) origin with average GI_{50} values of 23 and 14 μM [33]. The activation of the extrinsic apoptotic caspase-8 of polysaccharide-treated MDA-MB-231 induces apoptosis and causes cell death. The apoptotic signaling pathway was regulated via caspase-3, caspase-9, p53, Bax and Bcl-2 genes [34]. *Laurencia okamurai Yamada* derived seco-laurokamurone, four laurane-type sesquiterpenes, laurepoxylene, 3 β -hydroperoxyaplysin, 3-hydroperoxy-3-epiaplysin, and 8,10-dibromoisoaplysin, one laurokamurane-type sesquiterpene, laurokamurene D, and one bisabolane-type sesquiterpene, (5S)-5-acetoxy- β -bisabolene, induced cytotoxicity against HL-60 and A-549 human cancer cell lines (Table 2). These compounds studied displayed moderate activities, relative to controls [35]. It was for the first time found that *Laurencia okamurai* extract containing laurinterol (LOEL) exhibited an excellent effect on the induction of apoptosis as determined by DNA fragmentation, terminal deoxynucleotidyl transferase-mediated dUTP in situ nick-end labeling assay, cell cycle analysis, and measurement of activities of several caspases in melanoma cells. It was also demonstrated that transcriptional activation of p53, a tumor suppressor gene, and activation of p21 promoter by LOEL were involved in the induction of apoptosis by reporter gene assay. In particular, western blot analysis confirmed that LOEL above 5 $\mu\text{g}/\text{mL}$ significantly increased the expression level of phospho-p53, the active form. These results indicate that LOEL can induce apoptosis through a p53-dependent pathway in melanoma cells [36]. Seven different compounds named as cholesterol (1), cholesta- 5-en-3beta, 7alpha-diol (2), beta-stigmasterol (3) (Figure.2h), phytol (4), zeaxanthin (5), 4-hydroxybenzaldehyde (6), indolyl-3-carbaldehyde (7) isolated from *Laurencia tristicha*, within which cholesta- 5-en-3beta, 7alpha-diol shows promising activity against human cancer cell lines HCT-8, Bel-7402, BGc-823, A549 and HELA with IC_{50} values of 1.90, 2.02, 1.99, 6.52 and 1.20 $\mu\text{g mL}^{-1}$, respectively. Compound 4 showed cellular toxicity against HCT-8 and HELA with IC_{50} value of 3.51 and 2.04 $\mu\text{g mL}^{-1}$ [37]. T47D, ZR-75-1, and Hs578T 3 cancer cell lines were treated with terpenoid dehydro thyriferol that has been isolated from *Laurencia viridis* which also shows some cytotoxic effects [38]. Reports taken together suggests that the genus *Laurencia* have a wide range of phyto compounds of which few shows good anti cancer potential.

Lithothamnion

Lithothamnion is a genus of thalloid red alga comprising 103 species also commonly named as coralline algae. Cell food (CF) a nutrition rich supplement has been extracted from the organic and inorganic components of the red algae *Lithothamnion calcareum* which shows anti proliferative nature in *in-vitro* as well as *in vivo* model. CF remarkably inhibited leukemic cell viability by promoting cell apoptosis, as revealed by caspase-3 activation and DNA

laddering. CF treated cells showed lower HIF-1 levels and lower GLUT-1 expression as compared to untreated cells. CF also able to reduce LDH activity and as a result the amount of lactate released in the extracellular environment [39]. *Lithothamnion calcareum* extract contains 12% Ca^{2+} , 1% Mg^{2+} , and detectable amounts of 72 trace elements. The red algae extract was as effective as inorganic Ca^{2+} alone in suppressing growth and inducing differentiation of colon carcinoma cells that are responsive to a physiological level of extracellular Ca^{2+} (1.4 mM). However, with cells that are resistant to Ca^{2+} alone, the extract was still able to reduce proliferation and stimulate differentiation [40].

Lophocladia

Lophocladin B (Figure. 2f) isolated from red alga *Lophocladia* showed a remarkable cytotoxicity and cell cycle arrest of NCI-H460 human lung tumor and MDA-MB-435 breast cancer cell lines (Table 2). Cells in the G_1 and S phases with an accumulation of cells in G_2/M , signaling a G_2/M cell cycle arrest [41].

Porphyra

Porphyra is a cold water seaweed that grows in cold, shallow seawater. The polysaccharide extract of *Porphyra yezoensis* shows some anti proliferative activity on cancerous cell lines like SGC - 7901, 95D (Table 2) as documented by tetrazolium colorimetric assay [42]. Some researcher has also shown that *Porphyra yezoensis* can induce apoptosis through PI3K, PDK, Bad, mTOR Bcl, Bax. It also induces autophagy [43].

Solieria

Study reveals that incubation with methanolic extracts of *Solieria robusta* dramatically induce the cell cycle phase especially the sub G_1 accumulation of oral cancer cell line Ca9-22 (Table 2) detected by flow cytometry. Also it may over express the level of reactive oxygen species [44]. Mono galactosyl diacylglycerols (Figure. 2g) isolated from *Solieria chordalis* gives some anti proliferative effect in *in vitro* on human non-small-cell bronchopulmonary carcinoma cell line (NSCLC-N6) with an IC_{50} of 23 $\mu\text{g}/\text{mL}$ [45].

Symphyclocladia

2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (TDB) derived from *Symphyclocladia latiuscula*, have been tested on the proliferation of MCF-7 human breast cancer cells. Morphological characterization like nuclear membrane and DNA fragmentation under electron microscope shows apoptotic nature. It acts through Bcl-2 protein expression and the cleavage of caspase-3 substrates, with poly (ADP-ribose) polymerase cleavage occurring by TDB

treatment. TDB treatment also caused a drastically increase in the level of p21WAF1/CIP1 protein in a p53-dependent manner. Furthermore, the up gradation of p21WAF1/CIP1 in the MCF-7 cells (Table 2) was related to a decrease in c-Myc protein in a

dose-dependent manner. Based on the data reported, TDB is a good candidate for further evaluation as an effective chemotherapeutic agent, acting through the induction of apoptosis [46].

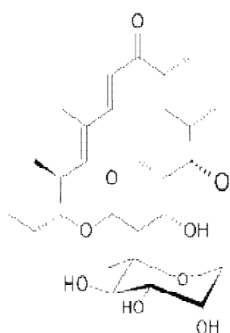


Fig.2a: Callophycin A

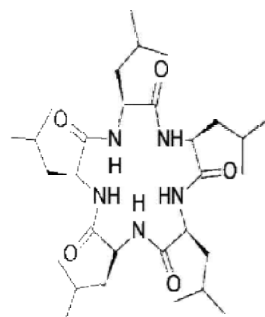


Fig.2b: Galaxamide.

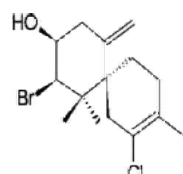


Fig.2c: Elatol.

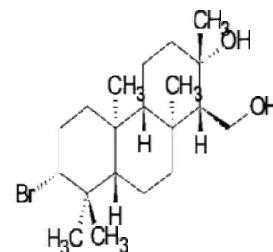


Fig.2d: Isoaplysin

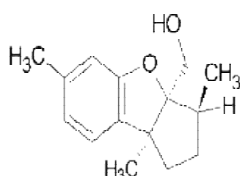


Fig.2e: Debromoaplysinol

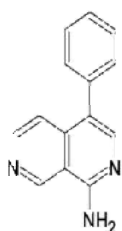


Fig.2f: Lophocladin B

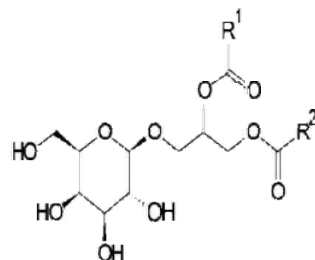


Fig.2g: Monogalactosyl Diacylglycerols

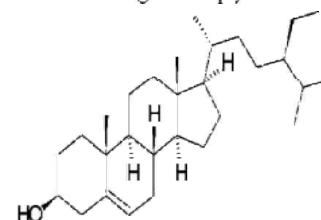
Fig. 2h: β -stigmasterol

Figure 2: Structure of anti cancer compounds derived from Red algae.

Table 2: List of Red algal species acting on different cancer cell types.

Name of the algae	Cell types	References
<i>Callophycus oppositifolius</i>	MCF 7 breast cancer cell proliferation	[20]
<i>Callophycus serratus</i>	BT-549, DU4475, MDAMD-468, MDA-MB-231, HCT-116, SHP-77 A549, PC-3, LNCaP-FGC, DU145, A2780/ DDP-S, CCRF-CEM	[21]
<i>Galaxaura oblongata</i>	HepG2, GRC-1, HuH-7, U937, HL-60	[22, 23, 24]
<i>Gelideilla acerosa</i>	A549, HCT-15, PC-3, MG-63	[25]
<i>Gelidium Amansii</i>	Hepa-1, NIH-3T3	[26]
<i>Gracilaria tenuistipitata</i>	Oral cancer cell	[27,28]
<i>Gracilaria edulis</i>	PC3	[29]
<i>Laurentia pacifica</i>	HT29, U87, SJ-G2, MCF-7, A2780, H460, A431, Du145, BE2-C, MIA, SMA	[33,34]
<i>Laurentia okamurai</i>	HL-60 and A-549	[35]
<i>Laurentia. tristicha</i>	HCT-8, HELA	[37]
<i>Laurentia viridis</i>	T47D, ZR-75-1, Hs578T 3	[38]
<i>Lophocladia sp.</i>	NCI H450, MDA-MB-435	[41]
<i>Porphyra yezoensis</i>	SGC -7901	[42,43]
<i>Solieria robusta</i>	Ca9-22	[44]
<i>Solieria chordalis</i>	NSCLC-N6	[45]
<i>Symphyocladia latiuscula</i>	MCF 7 breast cancer cell	[46]

Anti cancer compounds of Brown algae

Pheophyceae or Brown algae are mostly marine cold water species with some exceptions. Mainly xanthophyll pigment like fucoxanthin is present. It contains several long chained heteropolysaccharide, sugars and higher alcohols. Different genus of this group shows a high degree of anti proliferative properties. Some are mentioned below:

Colpomenia

Colpomenia is a marine brown algae commonly known as sea bubble, sinuous ball weed or oyster thief. Anti-leukemic activity is shown by the ethyl acetate extract from *Colpomenia* on hepatoma HUH 7 cells, leukemia U937 and HL-60 cells (Table 3). Condensed and fragmented DNA as well as Flow cytometrical data reveals that this cells treated with algal extracts shows apoptotic effects in dose and time dependent manner. Hydrogen peroxide, superoxide anion and several other intracellular reactive oxygen species acts as apoptotic agent which kills the leukemic cells 2-3 times [24].

Ecklonia

Ploroglucinol (Figure.3a), eckstolonol (Figure.3b), phlorofucofuroeckol A (Figure.3c), eckol (Figure.d3), dieckol (Figure.3e) are the five compounds, isolated from ethyl acetate soluble fraction of methanol extract of *Ecklonia stonifera* which acts as a inhibitor of total ROS generation [47]. *Ecklonia cava* has an important compound name as fucoidan (Figure. 3f) which is a

mixture of sulfated Rhamnogalactofucan and galactofucan. The report says that it is an effective anticancer agents and has a role to inhibit in colony formation in human melanoma and colon cancer cells [48]. Marine algae *Ecklonia cava* containing a compound named as phlorotannin (Figure.3g) guard the cells from radiation induced injury as well as oxidative stress [49]. Dieckol and phlorotannins (Figure.3g) are the two important compounds derived from *Ecklonia cava*, which demonstrates cytotoxic effects on A2780 and SKOV3 ovarian cancer cells (Table 3). Dieckol triggers the activation of Caspase8, 9, and 3. Pretreatment with caspase inhibitors neutralized the pro apoptotic activity of dieckol. Dieckol treatment causes mitochondrial dysfunction followed by suppression of anti apoptotic protein levels. Further demonstration says that dieckol actuate (induced) an increase in intracellular ROS, and the antioxidant N-acetyl-L-cysteine (NAC) significantly opposite the caspase activation, cytochrome c release, Bcl-2 downregulation, and apoptosis that were caused by dieckol. Moreover, dieckol obstructs the activity of AKT and p38, and overexpression of AKT and p38, at least in part, reversed dieckol-induced apoptosis in SKOV3 cells. These data give the idea that dieckol inhibits ovarian cancer cell growth by inducing caspase-dependent apoptosis via ROS production and the regulation of AKT and p38 signaling [50]. Phlorotannin-rich extract from the edible brown alga *Ecklonia cava* (PREC) combine with cisplatin downregulate the ROS/Akt/NFkB pathways and reduce nephrotoxicity by protecting against normal kidney cell damage [51], (Figure.4). Reports taken together reflects that *Ecklonia* is a potential repository of active bionolecules for the treatment of cancer.

Table 3: List of Brown algal species acting on different cancer cell types.

Name of the algae	Cell types	References
<i>Colpomenia sp.</i>	U937 HL-60 cells	[24]
<i>Ecklonia cava</i>	A2780, SKOV3	[47-51]
<i>Laminaria sp</i>	Colon, HeLa, colon Ht-29, HTLV	[52,53]
<i>Padina sp</i>	KB, Hep-2, MCF-7, and SiHa	[54]
<i>Sargassum sp</i>	Hela, MDA MB 231, Dalton's Ascitic lymphoma, HepG2, HT-29, Ca co-2, T47D, MDA-MB468 and /NIH 313,	[55- 60]
<i>Styopodium sp</i>	SH-SY5Y, RBL-2H3, (Raw267), (V79), Caco-2. DU-145	[53, 62]
<i>Undaria sp</i>	Leukemia, Breast, Lung	[63, 64]

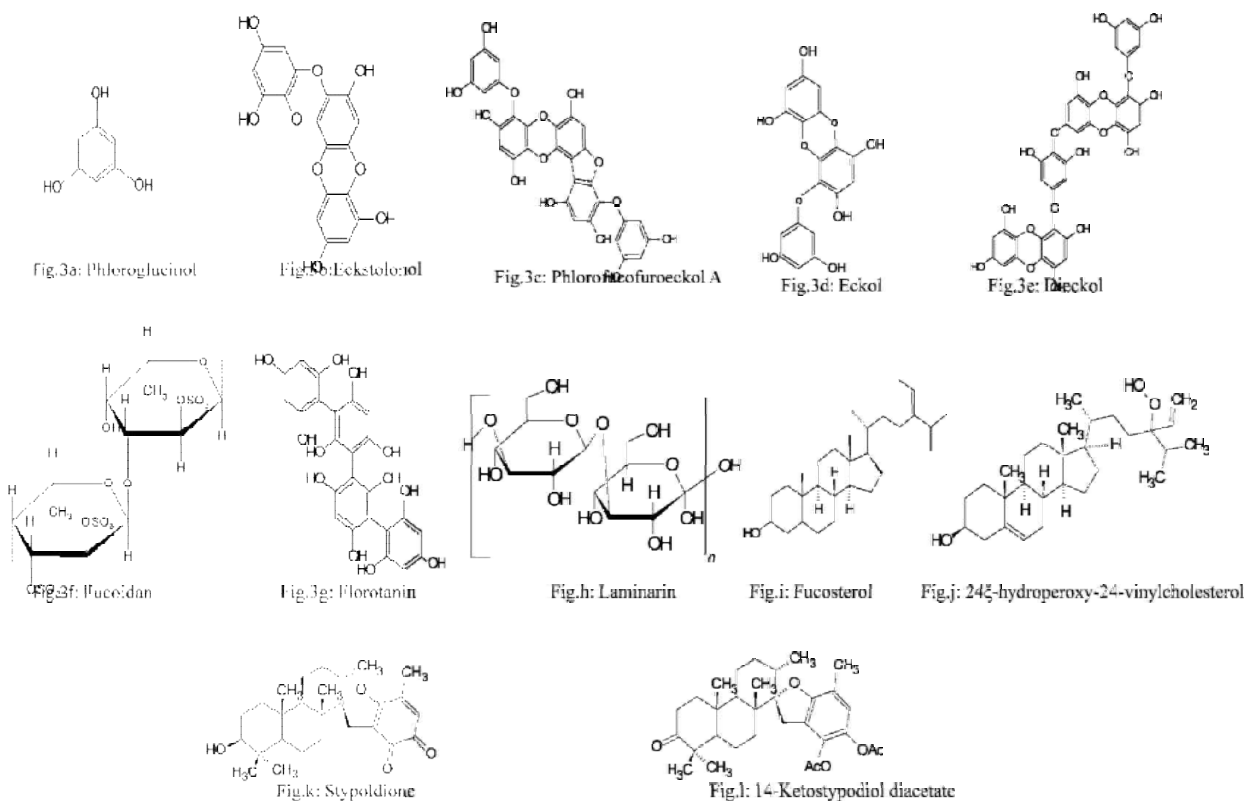


Figure 3: Structure of anti cancer compounds derived from Brown algae.

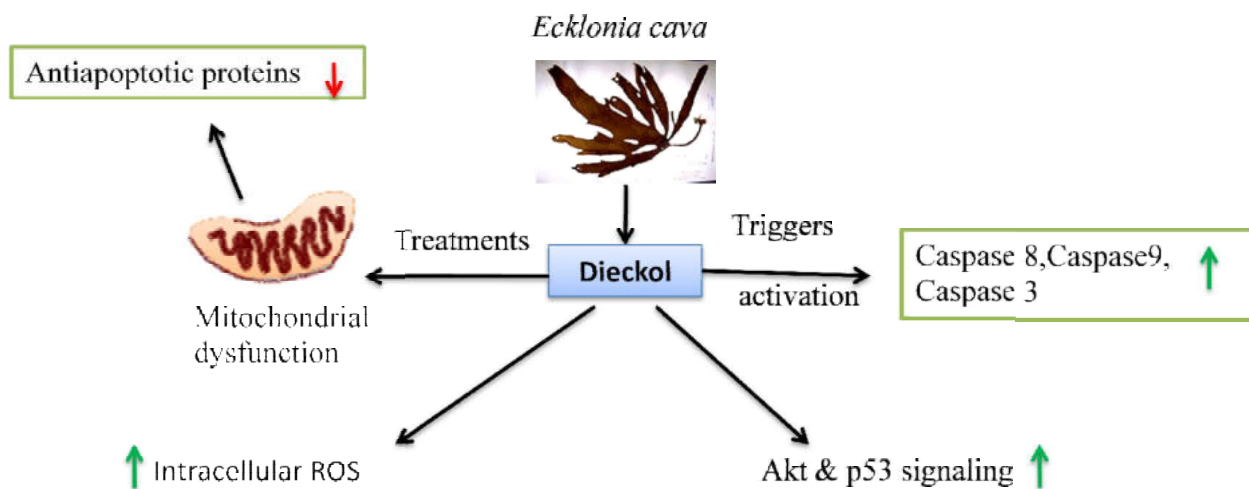


Figure 4: Mechanism of dieckol induced apoptosis on cancer cells isolated from *Ecklonia*. (Red) indicates down regulation, (Green) Upregulation. (Colour Figure)

Laminaria

Laminaria is one of the important genera under Pheophyceae. It is used as a traditional medicine in China. [52], whereas Japanese

use this sea weed as food, consumption of which decrease the risk of several cancer [53]. Reports say that Laminarin (Figure. 3h), a biopotent compound derived from *Laminaria* shows apoptotic effect in HT-29 colon cancer cells (Table 3) with the help of ErbB signaling pathway. Laminarin also up regulate the overall

percentage of cells in sub G1 and G2M phase in cell cycle. Laminarin inhibits the heregulin stimulated phosphorylation of ErbB2. ErbB by activating C-Jun-terminal kinase, decrease the proliferation rate. These findings reveal the important role of the epidermal growth factor receptor in colon cancer tumorigenesis [52]. Another case shows the effect of Laminarin on insulin like growth factor (IGF-IR) signaling pathway. Fas and Fas ligand receptor enhances the activation of caspases family members,

which leads to cleavage of apoptotic markers (PARP). Laminarin decreases Bcl-2 family protein expression, which in turn inhibited the cell cycle progression by resulting ErbB signaling pathway. HT-29 with Laminarin extracts inhibited phosphorylation and ErbB2 expression and phosphorylation of Akt (Figure.5). Data taken together clearly reflects that laminarin may be potent anti cancer drug in future.

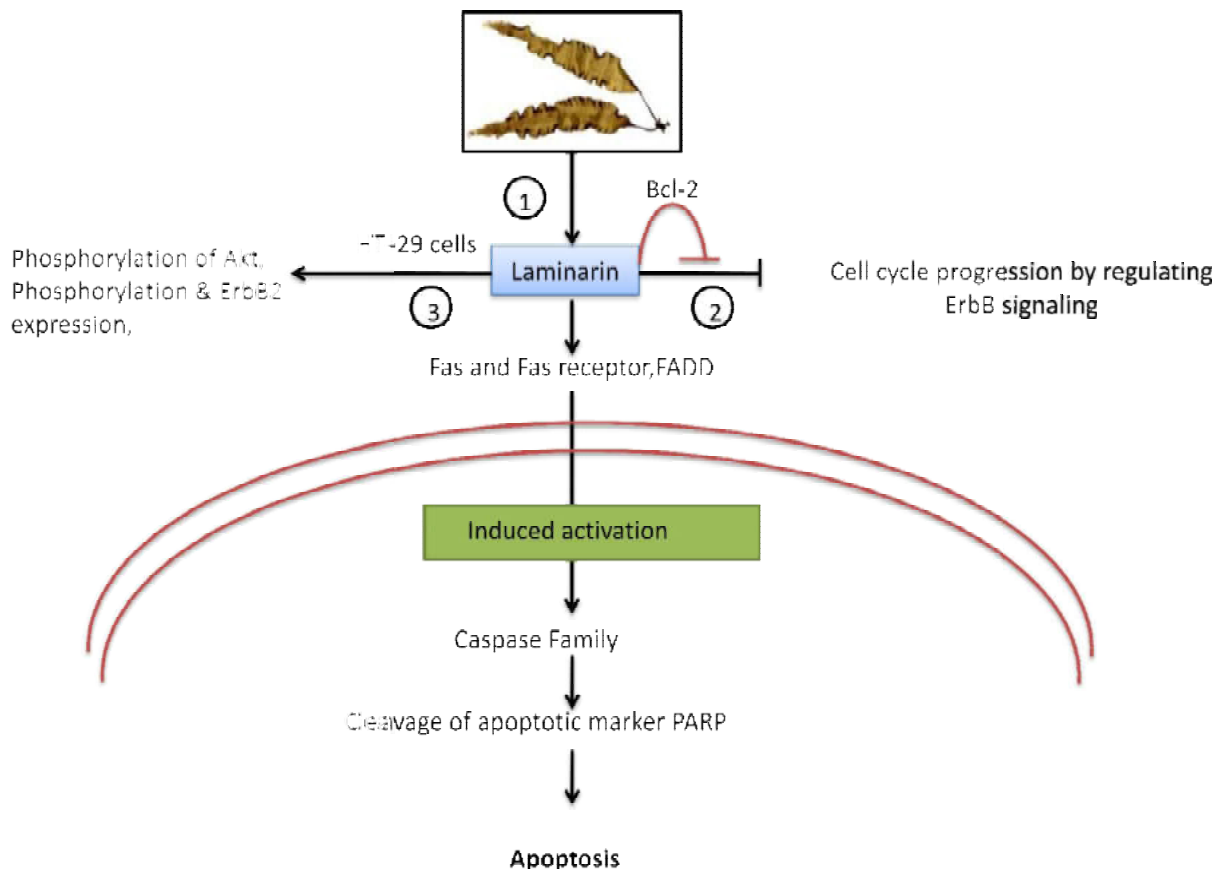


Figure 5: Mechanism of laminarin induced apoptosis isolated from *Laminaria*. (Colour Figure)

Padina

Padina is a well known brown sea algae commonly known as peacock's tail, scroll algae or potato algae. Hexane extracts of *Padina sanctae-crucis* shows anti proliferative and cytotoxic effects *in vitro*. Several compounds extracted from these brown algae, within which fucosterol (Figure. 3i) and 24 ξ -hydroperoxy-24-vinylcholesterol (Figure. 3j) were isolated from *Padina* sp. These two component shows anti proliferative effects on different cancer cell lines [54]. Other reports indicate that dichloromethane and ethyl acetate fractions of *Padina* sp. shows antioxidant activity.

Sargassum

Sargassum heterophyllum has anti proliferative activity against metastatic MDA-MB-231 breast cancer cells. SQA (Sargaquinoic acid) induces apoptosis while a polihalogenated monoterpene RU015 induced necrosis in metastatic breast cancer cells *in vitro* [55]. A compound fucoidan (Figure. 3f) isolated from *Sargassum horney* further fractionated into 3 groups homofucan sulfate, homofucan without sulfate group and a sulfated rhamnifucan. The fucoidan play an inhibitory role in colony formation in human melanoma and colon cancer cells and may be effective antitumor agents [48]. Sulfated galactofucan present in *S. henslowianum* indicates that unfractionated FCSPs may very much effective on

skin cancer cells via induction of apoptosis through cascades of reaction that involve activation of Caspase -3 [56]. To investigate the *in vitro* cytotoxic activity, extract of MeOH (70% & partition fractions of hexane, chloroform, ethyleacetate & MeOH- H₂O) of *S. swartzii* are used against HT-29, Ca co-2, T47D, MDA-MB468 and /NIH 313 cell lines. *S. swartzii* showed selective cytotoxicity against proliferation of Caco-2 cell [57]. Another species *Sargassum wightii* exhibited anti inflammatory effects [58]. Alcoholic extract of *S. ilicifilium* was tested against five human cancer cell line MCF-7, MDA-MB-231, HeLa, HepG2, HT-29 and the extract shows an anti proliferative effect against all the five cancer cell line in a dose regulated fashion [59]. Methanolic extracts of *S. muticum* was evaluated against MCF-7 and MDA-MB-231 breast cancer cell line (Table 3) and the extract showed anti proliferative activity [60]. Ethanolic extracts of *S. wightii* was very much effective against Dalton's Ascitic lymphoma. (DAL) [61].

Stypodium

Stypodium is an olive green or brownish golden coloured algae mainly found in shallow sea water or costal region. The different kinds of secondary metabolites have been isolated from this alga one of which is stypoldione (Figure. 3k) that has anti proliferative activity on lung cancer and colon cancer cell line. Study reveals that, six meroditerpenoids (epitaondiol, epitaondiol diacetate, epitaondiol monoacetate, stypotriol triacetate, 14-ketostypodiol

diacetate (Figure. 3l) and stypodiol isolated from the brown alga *Stypodium flabelliforme* exhibits a high degree of anti proliferative potentiality against SH-SY5Y (human neuroblastoma), Caco-2 (human colorectal adenocarcinoma), RBL-2H3 (rat basophilic leukemia) and RAW.267 (mouse macrophages) and towards V79 non-cancer cell line (Chinese hamster fibroblasts) cancer cell line, within which the human neuroblastoma cell line SH-SY5Y (Table 3) is the most susceptible towards these meroditerpenoids than all of the other cell lines, so indicating to the neurotoxicity of these secondary metabolites [62].

Undaria

Undaria is a large marine algae ranging from green to yellowish-brown to dark brown in colour. A fucose riched sulfated polysaccharide named as Fucoidan (Figure. 3), an important bioactive compound isolated from *Undaria*, exhibits proliferation, neoplastic transformation, and colony formation of mouse epidermal cells JB6 Cl41, human colon cancer DLD-1, breast cancer T-47D, and melanoma RPMI-7951 cell lines (Table 3), [63]. Another report highlighted on fucoidan, results that SMMC-7721 cells undergo apoptosis (Figure. 6) through up regulation of reactive oxygen species (ROS). That leads to oxidative detriment of mitochondrial ultra structure like membrane depolarization and several caspase activation [64].

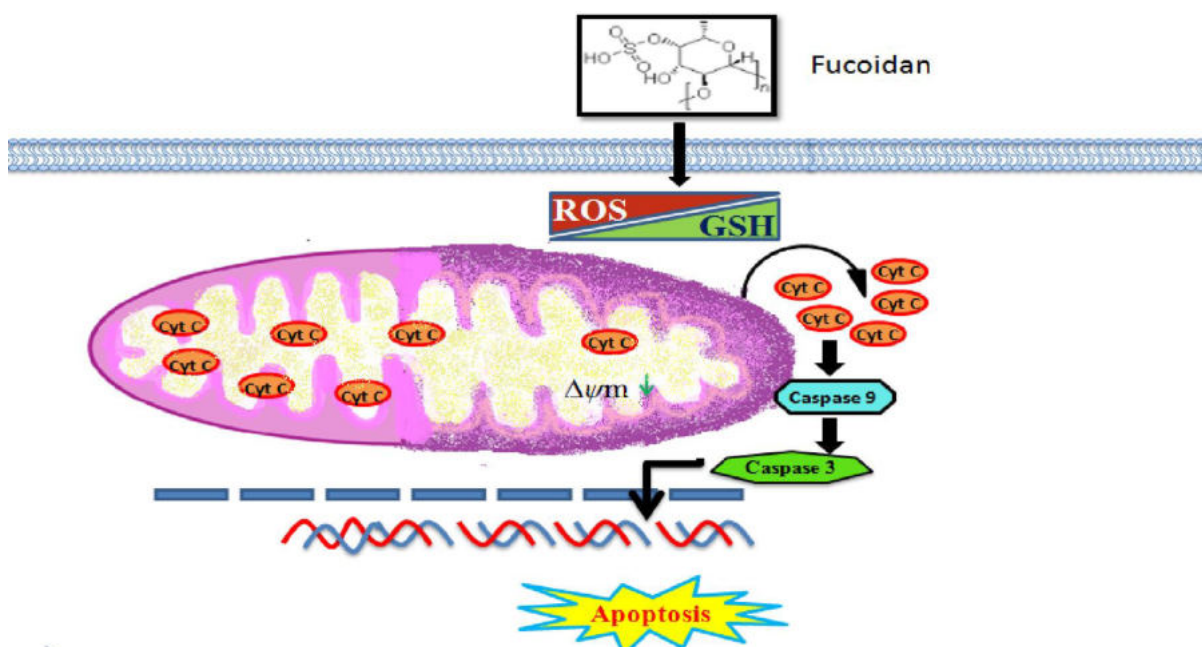


Figure 6: Effects of *Undaria* on *in vitro* SMMC-7721 cells. a) Fucoidan decreases the GSH level and increases the ROS level. b) Depolarisation of the mitochondrial membrane potentiality, mitochondrial swelling. c) The Cyt-C expel out from mitochondria that activates caspase 9 caspase 3, d) Within the nucleus the caspase 3 helps in apoptosis. (Colour figure)

Clinical trials

Some group of researcher has been attempt to make clinical trials beside *in vitro* analysis and received some satisfactory results. Noguchi *et al.*, performed to test the effects of the unicellular green algae *Chlorella* and hot water extract supplementation on quality of life (QOL) in patients with breast cancer in a self-control, randomized, and open-label clinical trial. Results indicate fifty percent of the *Chlorella* extract group reported positive effects by the test food such as reduction of fatigue and improvements of dry skin (versus control group). The findings suggested the beneficial effects of *Chlorella* on breast cancer-related QOL and of *Chlorella* extract on vitality status in breast cancer patients. Though these findings need to be confirmed in a larger study. Several other clinical trials were carried out with some species of algae [66].

Conclusion

Algae are found to be a natural repository of phyto-chemicals having anti-cancer activity. The phytochemicals isolated from different algal species reveal specific mechanism towards different cancer cell lines. In this article we have enlisted different algal species showing enhanced apoptotic and anti cancer activity in a

wide variety of cancer cells. This review focuses on the current examinations concerning the likely effects of bioactive components of algae on different types of cancer. Not only this report could be helpful for the present and future phycologist and oncologist, also it can enlighten the path of various unmasked cancer inhibiting algal sources in near future. It can be concluded from various reports that algae possess a golden treasure of various bioactive compounds for future development of anticancer drug discovery from nature. However, further in depth studies need to be performed to fully exploit its anticancer properties by looking at the different cell signaling pathways linked with cancer development.

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Author contribution

AM have collected information from different electronic sources, prepared initial design and wrote the manuscript, SP designed the review process and wrote the manuscript to the final form.

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