Original Article

Prolific Anticancer Bioactivity of Algal Extracts (Review)

Nadia Sharif*, Neelma Munir, Faiza Saleem, Farheen Aslam and Shagufta Naz

Department of Biotechnology, Lahore College for Women University, Lahore, Pakistan

Address for Correspondence

Department of Biotechnology, Lahore College for Women University, Lahore, Pakistan.
E-mail: nadiasharif.s7@gmail.com

SUMMARY

Now a days cancer incidences are in increasing trend and therefore instant effective therapies are needed to control these malignancies. Normally rapidly dividing cells are controlled by anti-cancer drugs, but the normal cells are also affected and pattern in which it is determines the side effects. The way in which the other cells are affected determines the side effects of the individual drugs. These side effects may be minimized by improving and new remedial preparations. These drugs could be of ethno botanical origin. Auspiciously numerous preceding readings have shown that the anti-cancer activities of non-toxic biological macromolecules are higher than conventional chemotherapy drugs. Marine algae is obliged as significant sources of natural bioactive substances and there has now emerged a new proclivity towards isolating and identifying such compounds and constituents from algae. This review article has poised studies about algal anticancer agents.

Keywords: Anticancer compounds, Cancerous cells, Inflammatory, Proliferative, Mutagenic.

CANCER DEVELOPMENT, CAUSES, AND TREATMENT

Cancer is most common and serious disease, it slaughters societies more than tuberculosis, malaria and HIV/AIDS combined[1]. A total of 12.5% of deaths worldwide is due to cancer and 12.1 million cancer cases were in 2007, 45% in developed countries and the remaining 55% in developing countries[2-4].

There are six properties that make cells capable of cancerous growth; they are not under the control of signals that regulate cell proliferation, they are resistant to apoptosis, they overcome the limitations on proliferation by avoiding replicative senescence and evading differentiation, they are genetically unstable, they are able to invade surrounding tissues and they are capable of metastasis[3, 5]. In order for a cancerous tumor to develop, cancer cells must overcome replicative cell senescence and become "immortalized" i.e. continue dividing indefinitely[6]. Tumors are only considered to be cancerous if they are capable of metastasis and colonizing

surrounding tissue[6,7]. Even though most cancers are thought to be monoclonal, cancer development takes place in many years by and involves several progressions. The original abnormal cell must undergo some change that allowed it to grow much faster than normal cells in the same tissue and this property had to be passed on to subsequent daughter cells. For cancer to successfully develop, numerous but independent changes must occur in this one cell[3,4,8].

Most cancers are thought to be a result of genetic mutations in the DNA of the cancerous cells and these mutations can be a result of inherited mutations, metabolism mutations, cigarette smoking, diet (red meat, fried foods), alcohol, radiation, environmental pollutants, and infectious organisms i-e viruses, stress, obesity, and physical inactivity. These causative elements might act in sequence or together to pledge or stimulate cancers[3,4,8].

Chemotherapy is usually the first line treatment to cure cancers. Besides that, a group of drugs are used to kill or inhibit the growth of cancer cells. These drugs are allied through noxiousness that range from a mild reaction to severe life-threatening illness. Many side effects of chemotherapeutic drugs comprised baldness, vomiting, Canker sores, diarrhea, loss of appetite, nausea and fatigue. Hence new anticancer agents should be investigated from various resources. A lot of natural antitumor amalgams or their byproducts are generally produced by blue-green algae[9].

BIOACTIVE MICROALGAL ANTICANCER PIGMENTS

Free radicals are involved in the induction of cancer formation in the human body. On the other side it has been noted that free radicals of vegetables and fruits doubles the protection against many types of cancers by scavenging activity[10]. Remarkable and exhilarating biological activities are displayed by microalgae like immunosuppressant, antitumor, anti-microbial and antiviral activities which are conspicuous targets of biomedical investigations[11]. Bioactive molecules with anticancer activities are one major group of targeted compounds from microalgae. Hence, there is a need to extract natural bioactive amalgams from algae.

More than 50 % of marine cyanobacteria are possibly available for intending bioactive elements which are powerful in either slaughtering the disease cells by instigating apoptotic demise, or influencing the cell signaling over the enactment of the portions of protein kinase-c group of indicating chemicals. Isolation of cytotoxic antitumor substances from marine organisms has been reported in several references during the last 40 years, while in recent years, hundreds of potential anti tumour agents have been isolated from marine origin especially from marine algae and[12].

Compounds obtained from marine algae have assumed a vital part in the improvement of a few clinically valuable anticancer managers. In most cases, the evaluation of anticancer potential of crude extracts from different sea organisms has been carried out by *in vivo* cytotoxicity tests in malignant cell cultures. The capacity of algal polysaccharides to incite cancer cell multiplication has been overall recorded. The epidemiological information is upheld by rat model studies exhibiting defensive impacts of dietary kelps and other red and green algae against mammary tumors[13]. Molecular and cellular level studies on algae have indicated that algae derived bioactives are potent cancer inhibitors. Documentation of new active cancer inhibiting agents have globally turn out to be a significant strategy[14].

A variety of red algae as well as kelp has anti proliferative and anti-inflammatory activities. *In vivo* and *in vitro* studies on seaweed constituents have been conducted to explicate the antimutagenic mechanisms of underlying the potential anticarcinogenic effects of kelp and red algae against colon and breast cancers[15,16]. Some anticancer agents of algal source are:

Polysaccharides

Polysaccharides are utmost bounteous amongst the characteristic natural bioactives produced by plants and they are generally present in algae, animals, microorganisms and plants[17,18]. Polysaccrides are polymeric carbohydrate structures that are formed by monosaccharides linked by different glucosidic[19]. Distinctive functional properties of polysaccharides are because of their structure organized by their building blocks[20]. Compared the *Ecklonia cava* polysaccharide compounds with commercial counterparts (BHA and BHT) and found that due to the high amount of polyphenol contents it can suppress cancer cell proliferation. The polysaccharides isolated from *Spirulina* sp. enhanced excision, unscheduled DNA synthesis, radiation damaged DNA repair activity and exhibited enhanced activity of endonuclease significantly. DNA synthesis of sarcoma 180, ascetic hepatoma cells and proliferation of ascitic hepatoma cells of mice is also inhibited by it[21].

Calcium spirulina (Ca-SP) is a polysaccharide of *Spirulina platensis* inhibited tumor invasion and metastasis[22]. Observed that the acidic polysaccharides in *S. platensis* are involved in macrophage - tumor necrosis factor- (TNF-) dependent tumoricidal activity[23]. Found that the *Spirulina* polysaccharides suppress the glioma cell (murine RSV-M) growth via partial regulation of interleukin-17 production and down regulating angiogenesis. It was also noticed that the selenium nanoparticles (SeNPs) with *Spirulina* polysaccharides (SPS) may be potential candidates against human cancers as chemo preventive and chemotherapeutic agents[24] and polysaccharide from *Porphyra yezoensis* are useful in the treatment of human cancers[25].

Polysaccharides extracted from Japanese kelp like *Undaria pinnatifida, Hijikia fusiforme*, *Laminaria japonica* and *Eisenia bicyclis* were recognized as forthcoming hostile to genotoxic elements. Polysaccharides extricated from the brown algae, *Sargassum latifolium* have significant antitumor action against leukemia[26].

Fucoidans

Polysaccharides - fucoidans that are consisted of sulfated Lfucose with short of what 10 % of different monosaccharides. Fucoidans are present in the cell walls of brown seaweed[27]. Fucoidan has antiproliferative activities, although its complete mechanism is yet not known. In a study of[28] 10 mg/kg fucoidan was proved effective against metastatic tumor when it was administered in Lewis lung adenocarcinoma affected mice.

Tumor size and growth could be controlled by the polyanionic polysaccharides due to their antiproliferation and anti-angiogenesis actions towards tumor cells[29]. These substances are also involved in anti-cancer activity through ERK and caspase pathways against human HS-Sultan cells[30]. Fucoidans are also able to enhance the immunomodulatory activity to restrain the diffusion and development of tumour cells as they mediate the destruction of tumors by NK cell and type 1 T helper (Th1) cell responses[31]. When fucoidan is used at 25 mg/kg dose, several types of auto-immune disorders and tumors are reduced due to the cyclophosphamide toxic effect[28].

Due to antiproliferative bioactivity, *fucoidan* is also noted as an active principal of CpoF. This sulfated polysaccharide is composed of fucose with small amount of galactose. Molecular weight and sulfate contents are directly related to their anticancer activity. It is documented that the anticancer activity of fucoidans is increased when it is hydrolyzed for 5min with HCl in boiling water. Conversely the anticancer activity is slightly improved when fucoidans are hydrolyzed in a microwave oven. So it is concluded that fucoidans anticancer activity might be enhanced considerably by lowering the molecular weight when they are depolymerized at mild conditions[32].

Fucoidan was tested for its efficiency and it was found that it increases Smac/Diablo and cytochrome c release from the mitochondria as well as its enhanced mitochondrial membrane permeability. It was also observed that the levels of Mcl-1 decreased, whereas death receptor 5 proteins, truncated Bid proteins, TRAIL, Fas, and Bak were increased in fucoidan treated cells[33].

Phycocyanin (PC)

Phycocyanin is currently used in Japan and China as a regular coloring agent in dairy and dietary products like gums, candies, jellies, beverages (*e.g*. Pepsi® blue and also in cosmetics such as lipsticks, eyeliners and eye shadows. Phycocyanin is light and heat sensitive, but it is a more epitome blue colorant than indigo and gardenia and it gave more bright blue color in jellies and candies[34]. Algal Phycocyanin is also useful in the treatment of different types of cancers[25].

The phycocyanin isolated from *S. platensis* exhibited anticancer activity against squamous cell carcinoma. C-phycocyanins (C-PC) is a major biliproteins of *S. platensis* has radical scavenging and antioxidant properties. It exhibits anti inflammatory and anticancer properties and prompts *in vitro* apoptosis[35]. The increased phycocyanin of *S. platensis* induces apoptosis by the expression of CD59 proteins in HeLa cells[36]. The apoptosis is induced by C-PC in HeLa cells by activating apoptosis enzymes, caspases 2, 3, 4, 6, 8, 9, and caspase - 10. The cytochrome c that is released from the mitochondria into the cytosol cause C-PC-treated HeLa cell apoptosis (*in vitro*). The survival rate of mice with live tumor cells is increased by the oral administration of PC of *Spirulina* and *S. platensis* C-phycocyanin (C-PC) inhibit the growth and cell viability of human leukemia K562 cells. PC is a potential cancer chemopreventive[37].

Spirulina platensis (selenium-enriched) derived selenium-containing phycocyanin (Se-PC) is a strong anticancer agent on human breast adenocarcinoma MCF-7 cells and human melanoma A375 cells. The Se-PC induces apoptosis by accumulation of sub-G1 cells, and nuclear condensation, DNA fragmentation in both MCF-7 cells and A375[38]. *Spirulina platensis* display potential effect on the immune system and immune response and it contributes some extent in treating diseases and killing of cancerous cells.

The purified c-phycocyanin and polysaccharides of *Spirulina platensis* influence the proliferation and differentiation of committed hematopoietic progenitor, can lower the anemic degree of mice. and enhances the immune response by activating macrophage functions, IL - I production, phagocytosis and particularly by primary. Therefore the part of *PC* to enhance efficiency of the immune response is important in treatments and prevention of all types of cancers[39].

Chlorophyll

Carotene, chlorophyll and lutein related compounds derived from algae

strains have been accounted for solid ant proliferative bioactivity *in vitro* and *in vivo*. Tumor preventive impacts of chlorophyll and its subordinates have been widely concentrated on, with specific accentuation on their *in vitro* anticarcinogenic impact against various ecological and dietary mutagens. Chlorophyll-a and chlorophyllin-a have displayed huge concealment against the instigation of ornithine decarboxylase in mouse skin fibroblasts created by a tumor promoter utilizing with*in vitro* cell culture tests[40,41].

Pheophytin

Pheophytin, secluded from *E. prolifera* accounted for to illustrate the strong oppressive impact against artificially affected mouse skin tumorigenesis from end to end concealment at launch and limited time stages. *E. prolifera* derived Pheophytins also exhibited higher suppressive activity than chlorophyll a in *S. typhimurium* and mouse skin tumorigenesis[20,41,42].

Carotenoids

Natural fat-soluble pigments known as carotenoids, provides bright pigmentation to and animals plants. Numerous carotenoids, in the same way as a-carotene, astaxanthin, beta-carotene, zeaxanthin, lycopene, canthaxanthin, beta-cryptoxanthin, lutein and fucoxanthin have been demonstrated to have against cancer-causing action in a few tissues. Preclinical studies have demonstrated that a few carotenoids have powerful anticancer impacts both *in vitro* and *in vivo* models. Since chemoprevention is a standout amongst the most critical methodologies in the control of malignancy improvement, sub-atomic component based disease chemoprevention utilizing carotenoids appears to be an alluring methodology (Tanaka *et al*., 2012).

β Carotene

One of the utmost recognized important active antitumor agents are beta carotene. *Spirulina* is very rich in beta-carotene. Beta carotene significantly inhibits the formation of squamous cell carcinoma. *Spiulina, Dunaliella* algae prevents tumor development. Studies related to use of beta carotene on animals indicated slighter however, statistically momentous decrease in tumor size and number.

Fucoxanthin

A brown algae carotenoid known as fucoxanthin is recognized to exhibit potential antitumor activity. It also abridged the human colon cancer cell lines by inducing the fragmentation of DNA. Fucoxanthin is involved in decreasing the apoptosis suppressing protein (Bcl-2) level, it induced apoptosis in human prostate cancer cells (PC-3, DU 145 and LNCaP) [43,44]. In a re-sensitizing test for drugs it was found that fucoxanthin overcome drug resistance[45]. Though the complete mechanism is yet not known, but according to researchers in several cancer cells apoptosis may be induced by the prooxidant actions of oxygen, alkali and acids with double bonds and 5, 6-monoepoxide of fucoxanthin[33,41].

Compared[46] and found that the inhibitory activity of fucoxanthinol and fucoxanthin was higher than astaxanthin and b-carotene. It was observed that fucoxanthin induced apoptosis in human leukemia cells (HL-60) by activation of central executioner of the apoptotic pathway that is caspase-3, -8 and -9[44].

Siphonaxanthin

A marine carotenoid Siphonaxanthin derived from green growth has as of late been exhibited to lessening outflow of Bcl-2 and astoundingly upgraded initiation of

caspase-3 alongside up-controlled representation of Gadd45α and Dr5 in human leukemia (HL-60) cells. They have additionally reported that siphonaxanthin inferred from *Codium fragile* are more strong development inhibitor against HL-60 cells than fucoxanthin (Farooqi *et al*., 2012b; Ganesan *et al*., 2011a).

The structural contrasts between these two carotenoids are fucoxanthin contains epoxide and an allenic bond in its structure, though siphonaxanthin does not contain those useful gatherings; notwithstanding, siphonaxanthin has an extra hydroxyl gather on the nineteenth carbon iota. Since esterified type of siphonaxanthin indicated lower inhibitory impact, recommending that the vicinity of that hydroxyl gathering is helping the solid inhibitory impact of siphonaxanthin (Ganesan *et al*., 2011a). In the meantime, hostile to proliferative impact and apoptosis affectation by fucoxanthin in human colon malignancy cells (Caco-2, HT-29 and DLD-1) were seen by (Hosokawa *et al*., 2004).

Pheophytin

Pheophytin, segregated from *E. prolifera* has been accounted for to show the powerful suppressive impact against artificially instigated mouse skin tumorigenesis through concealment at the start and special stages (Athukorala *et al*., 2006b).

E. prolifera determined Pheophytins showed higher suppressive action in *S. typhimurium* and mouse skin tumorigenesis than chlorophyll a. These discoveries, recommend that porphyrin mixes determined marine green growth may have a vital chemopreventive movement against carcinogenesis (Pangestuti and Kim, 2011).

Benzochromenone

Benzochromenone is a colorant acquired from a dynamic concentrate of the marine crinoids *Comantheria rotula* utilizing Bioassay-guided fractionation and altogether repressed hypoxia instigating component (HIF) action, however, vascular endothelial development variable (VEGF), the target quality of HIF was not significantly curbed. In any case these crinoids colors differentially stifled the development of certain tumor cell lines (Dai *et al*., 2006).

Sodwanone a triterpenoid from a South African type of the marine wipe was additionally tried to be powerful in restraining HIF-1 initiation in PC-3 prostate tumor cells (Dai *et al*., 2007).

Stypodiol diacetate

14-keto-stypodiol diacetate is a medication extricated from the green growth Stypopodium *flabelliforme* and was demonstrated to upset microtubular association furthermore restrained cell expansion in DU-145 human prostatic cells[47].

Glycoprotein

Glycoprotein of *Capsosiphon fulvescens*, green ocean green growth impels apoptosis in human gastric tumor (AGS) cells Kim *et al*. Fucose-containing sulfated polysaccharides (Fcsps) extricated from tan macro-green growth is likewise archived to affect apoptosis[48, 51].

Investigations of tan green growth have demonstrated that glycoproteins from *Laminaria japonica* and fucoidans from *Sargassum hornery*, *Eclonia cava*, and *Costaria costata* had hostile to disease impacts on human colon malignancy cells. Heterofucans from Sargassum filipendula showed against proliferative consequences for cervical, prostate, and liver growth cells. A carotenoid fucoxanthin cool restrain the development of Lncap prostate growth cells by capturing these phones in the G1 stage by means of the Gdd45a and SAPK/JNK

pathways. Investigations of blue green growth have affirmed the opposition to disease impacts of *Spirulina* arrangements recombinant glycoproteins, particularly microcystis viridis lectin (MVL), and cryptophycin[52-54].

Meroditerpenoids

Viability of meroditerpenoids segregated from the tan alga *Stypopodium flabelliforme* were tried and it was exhibited that it demonstrates impressive movement against distinctive disease cell lines (Areche *et al*., 2009b; Gamal and Ali, 2010; Pereira *et al*., 2011). Meroterpenoids are of blended biogenesis containing terpenoid and non-terpenoid inferred parts. This wide definition could incorporate the immense number of straightforward prenylated phenolics yet is typically held for mixes where the terpenoid section embodies a huge piece of the atom. The polyprenylated quinones and chromanols typified by the ubiquinones and tocopherols are plainly of blended biogenesis yet the metabolites of *Aspergillus ustussuch* as Austin could be mixed up for sesterterpenoids. Truth be told these metabolites have been demonstrated to be inferred from a sesquiterpenoid part and a sweet-smelling polyketide piece[55.]

Stypotriol triacetate

This polycyclic meroditerpenoid, the complete setup of which was as of late decided, was likewise separated from the kelp *Stypopodium flabelliforme* (Areche *et al*., 2009a).

Yessotoxins

Yessotoxins (YTXs) are a gathering of lipophilic sulfated polyether intensifies that are structurally identified with brevetoxins and ciguatoxins. They are delivered by various algal strains, especially the *Protoceratium reticulatum*, *Lingulodinium polyedrum*, *Gonyaulax spinifera* and dinoflagellates. At the point when the natural conditions empower the development of these algal species, YTXs can aggregate in the water supply and inside the palatable tissues of bivalve molluscs, including scallops, mussels, and mollusks, consequently empowering the passage of YTX into the evolved way of life. Yessotoxins acquired from red tide green growth, *Protoceratium reticulatum* are successful regarding affectation of apoptosis[56,57].

Elatol

Elatol also have antitumor activity and various studies have confirmed that *Laurencia microcladia* derived elatol reduces tumour growth in C57BL6 mice[48,58].

Bis (2, 3-dibromo-4, 5-dihydroxybenzyl) ether (BDDE)

BDDE bromophenol compound that obtained from marine algae have persuasive apoptotic activity in K562 cells[48,59].

Sargachromanol E (SE)

SE, chromene derived from *Sargassum siliquastrum* inhibit HL-60 cells at a specific concentration. The compound was additionally noted to impel apoptosis by means of caspase 3 enactment[60]. Kelp and red algal extracts have potential anti-carcinogenic and antimutagenicity against breast and colon cancer[16,61].

Cannabinoids

Conventional chemotherapies produce toxic effects, but Cannabinoids do not produce such effects and these are usually well tolerated. Cannabinoids of *Cannabis sativa* stimulate appetite and prevent vomiting; pain and nausea in cancer patients so have palliative effects. These compounds also modulate key cell-signalling pathways to inhibit the growth of tumour cells in animal models and culture[62].

Triprenylated toluquinones and toluhydro-quinones

Leminda millecra and *Arminacean nudibranch* derived toluhydroquinones and triprenylated toluquinones are involved in apoptosis of esophageal cancer cells[63].

Monoterpenes

Monoterpenes (e.g., linalool) are used as flavors/fragrances in food additives. Camphene, α-pinene and monoterpenes which are produced by numerous plants are involved in inhibiting the early root growth and seed germination in several plant classes[64,65]. Halogenated monoterpenoids are also found in many marine organisms. It has been revealed by studies that algal Quinones and halogenated monoterpenes are enable to prompt *in vitro* apoptosis in breast cancer cells[66].

Halogenated monoterpenes are also produced by *Plocamium*, *Porteria* and *Ochtodes* algal species. Halogenated monoterpene, isolated from *Portieria hornemannii*, containing both bromine and chlorine groups was shown to have high levels of cytotoxicity against brain, colon and kidney tumours. Species of the *Plocamium* genus produce both linear and cyclic halogenated monoterpenes as secondary metabolites[67]. These compounds have been demonstrated as having anti-cancer activity in human oesophageal cancer cell line WHCO1[68,69]. In another study, four halogenated monoterpenes from *Plocamium cartilagineum* showed anti-cancer activity against colon adenocarcinoma cell line SW480 and cervical adenocarcinoma cell line HeLa but showed no toxic effects against non-cancerous Chinese hamster ovary cell line[70].

With respect to breast cancer, some monoterpenes act by interfering with signal transduction pathways, thereby changing gene expression and resulting in tumor regression. Some monoterpenes have been patented as potential chemotherapeutic drugs and in addition to having anti-cancer activity these compounds are also capable of sensitizing select tumors to radiation[71]. (See table 1.)

CONCLUSION

Chemotherapeutic agents are unable to completely control the cancer stem cells, which are inherently resilient and become repopulated subsequent to chemotherapy. But only few or no side effects are observed when natural anticancer agents are used. Therefore, the prevention of cancers by the identification of distinctive cancer chemotherapeutic has turn out to be a vital worldwide approach. This mini review was made to convey the glare of publicity of current examinations concerning the likely effects of bioactive components of algae on cancer. It can be concluded from previous studies on algae cancerous bioactivity that microalgae is probable to develop anticancer drug as it is a product of nature. However, further studies need to be performed to fully exploit its anticancer properties such as determination of the nature of cell death caused by the extract or visual detection and confirmation of apoptosis.

ACKNOWLEDGEMENT

The authors want to thank the financial supports from “Higher Education Commission (HEC)” Pakistan (1500006861/ 3244).

REFERENCES

1. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD, Dirks PB. Identification of human brain tumour initiating cells. *Nature* 2004; 432(7015): 396-401.
2. Bao S, Wu Q, Sathornsumetee S, Hao Y, Li Z, Hjelmeland AB, Shi Q, McLendon RE,

Bigner DD, Rich JN. Stem cell–like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. *Cancer research* 2006; 66(16): 7843-7848.
3. Bertram JS. The molecular biology of cancer. *Molecular aspects of medicine* 2000; 21(6): 167-223.
4. Garcia M, Jemal A, Ward E, Center M, Hao Y, Siegel R, Thun M. Global cancer facts & figures 2007. *Atlanta, GA: American Cancer Society* 2007; 1(3).
5. Fleming S. The molecular biology of cancer: the basics. *Surgery (Oxford)* 2003; 21(11): iii-vi.
6. Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J. Cancer: a systems biology disease. *Biosystems* 2006; 83(2): 81-90.
7. de Castro Junior G, Puglisi F, de Azambuja E, El Saghir NS, Awada A. Angiogenesis and cancer: a cross-talk between basic science and clinical trials (the "do ut des" paradigm). *Critical reviews in oncology/hematology* 2006; 59(1): 40-50.
8. Hart IR. Biology of cancer. *Medicine* 2004; 32(3): 1-5.
9. Patterson GM, Larsen LK, Moore RE. Bioactive natural products from blue-green algae. *Journal of Applied Phycology* 1994; 6(2): 151-157.
10. Singh N, Rajini P. Free radical scavenging activity of an aqueous extract of potato peel. *Food Chemistry* 2004; 85(4): 611-616.
11. Luesch H, Harrigan G, Goetz G, Horgen F. The cyanobacterial origin of potent anticancer agents originally isolated from sea hares. *Current medicinal chemistry* 2002; 9(20): 1791-1806.
12. Zanchett G, Oliveira-Filho E, C., Cyanobacteria and Cyanotoxins: From Impacts on Aquatic Ecosystems and Human Health to Anticarcinogenic Effects. *Toxins* 2013; 5(10): 1896-1917.
13. Funahashi H, Imai T, Mase T, Sekiya M, Yokoi K, Hayashi H, Shibata A, Hayashi T, Nishikawa M, Suda N. Seaweed prevents breast cancer? *Cancer Science* 2001; 92(5): 483-487.
14. Sithranga B, N., Kathiresan K. Anticancer drugs from marine flora: an overview. *Journal of oncology* 2011; 2010.
15. Yuan Y, V., Walsh N, A., Antioxidant and antiproliferative activities of extracts from a variety of edible seaweeds. *Food and Chemical Toxicology* 2006; 44(7): 1144-1150.
16. Berge J, Debiton E, Dumay J, Durand P, Barthomeuf C. *In vitro* anti-inflammatory and anti-proliferative activity of sulfolipids from the red alga Porphyridium cruentum. *Journal of agricultural and food chemistry* 2002; 50(21): 6227-6232.
17. Paulsen BS. Biologically active polysaccharides as possible lead compounds. *Phytochem Rev* 2002; 1: 379-387.
18. Yang L, Zhang LM. Chemical structure and chain conformational characterization of some bioactive polysaccharides isolated from natural sources. *Carb Polym* 2009 76: 349-361.
19. Holdt SL, Kraan S. Bioactive compounds in seaweeds: functional food applications and legislation. *J Appl Phycol* 2011; 23 543-597.
20. Athukorala Y, Kim K-N, Jeon Y-J. Antiproliferative and antioxidant properties of an enzymatic hydrolysate from brown alga, *Ecklonia cava*. *Food and Chemical Toxicology* 2006; 44(7): 1065-1074.
21. Ranjani R. Anticancer properties of blue green algae *Spirulina platensis* - A Review. *International Journal of Medicine and Pharmaceutical Sciences* 2013; 3(4): 159-168.
22. Parages ML, Rico RM, Abdala D, R. T., , Chabrill M, Sotiroudis TG, Jim eC. Acidic polysaccharides of Arthrospira (Spirulina) platensis induce the synthesis of TNF- α. in RAW macrophages. *Journal of Applied Phycology* 2012 24: 1537-1546.
23. Kawanishi Y, Tominaga A, Okuyama H. Regulatory effects of Spirulina complex polysaccharides on growth of murine RSV-M glioma cells through Toll-like receptor-4. *Microbiology and Immunology* 2013; 57(1): 63-73.
24. Fang Y, Quanming T, Xueyun Z, Yan B, Tianfeng C, Yibo Z, Yinghua L, Wenjie Z. Surface decoration by Spirulina polysaccharide enhances the cellular uptake and anticancer efficacy of selenium nanoparticles. *International Journal of Nanomedicine* 2012; 7: 835-844.

25. Lu Xi Z, Chun E, Cai., , Ting T, Guo.,, Jia W, Gu., , Hong L, Xu., , Yun Z, Yuan W, Cheng C, Liu.,, Pei M, H., . Anti-cancer effects of polysaccharide and phycocyanin from porphyra yezoensis, *Journal of Marine Science and Technology* 2011; 19(4): 377-382.
26. Gamal-Eldeen AM, Ahmed EF, Abo-Zeid MA. *In vitro* cancer chemopreventive properties of polysaccharide extract from the brown alga, *Sargassum latifolium*. *Food Chem Toxicol* 2009; 47(6): 1378-1384.
27. Berteau O, Mulloy B. Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. *Glycobiology* 2003; 13(6): 29-40.
28. Alekseyenko TV, Zhanayeva SY, Venediktova AA, Zvyagintseva TN, Kuznetsova TA, Besednova NN. Antitumor and antimetastatic activity of fucoidan, a sulfated polysaccharide isolated from the Okhotsk sea *Fucus evanescens* brown alga. *Bulletin of Experimental Biology and Medicine* 2007; 143(6): 730-732.
29. Li Y, Qian ZJ, Le QT, Kim MM, Kim SK. Bioactive phloroglucinol derivatives isolated from an edible marine brown alga, *Ecklonia cava*. *Journal of Biotechnology* 2008; 136: 578.
30. Liu RM, Bignon J, Haroun-Bouhedja F, Bittoun P, Vassy J, Fermandjian S. Inhibitory effect of fucoidan on the adhesion of adenocarcinoma cells to fibronectin. *Anticancer Research* 2005; 25(3): 2129-2133.
31. Maruyama H, Tanaka M, Hashimoto M, Inoue M, Sasahara T. The suppressive effect of Mekabu fucoidan on an attachment of Cryptosporidium parvum oocysts to the intestinal epithelial cells in neonatal mice. *Life Sciences* 2007; 80(8): 775-781.
32. Yang C, Chung D, Shin I-S, Lee H, Kim J, Lee Y, You S. Effects of molecular weight and hydrolysis conditions on anticancer activity of fucoidans from sporophyll of< i> Undaria pinnatifida</i>. *International journal of biological macromolecules* 2008; 43(5): 433-437.
33. Kim S-K, Pangestuti R. 9 Biological Activities and Potential Health Benefits of Fucoxanthin Derived from Marine Brown Algae. *Advances in food and nutrition research* 2011; 64: 111.
34. Jespersen L, Stromdahl LD, Olsen K, Skibsted LH. Heat and light stability of three natural blue colorants for use in confectionery and beverages. *Eur Food R Technol* 2005 220 261-266.
35. Reddy MC, Subhashini J, Mahipal SVK. C-Phycocyanin, a selective cyclooxygenase – 2 inhibitor, induces apoptosis in lipopolysaccharides stimulated RAW 264.7 macrophages. *Biochemical and Biophysical Research communications* 2003; 304(2): 385 - 392.
36. Li B, Zhang X, Gao M, Chu X. Effects of CD59 on antitumoral activities of phycocyanin from *Spirulina platensis*. *Biomedicine and Pharmacotherapy* 2005 59 (10): 551-560.
37. Li W, Wu FC, Fu PQ, Liu CQ, Wang J, Mei Y, Wang LY, Bai YC. Profile characteristics and seasonal variation of dissolved organic matter in Hongfeng Lake, Guizhou. *Huan Jing Ke Xue* 2006; 27(10): 1979-1985.
38. Chen T, Wong YS. *In vitro* antioxidant and antiproliferative activities of selenium-containing phycocyanin from selenium-enriched Spirulina platensis. *J Agric Food Chem* 2008; 56(12): 4352-4358.
39. Ozao-Choy J, Ma G, Kao J, Wang GX, Meseck M, Sung M, Schwartz M, Divino CM, Pan P-Y, Chen S-H. The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. *Cancer research* 2009; 69(6): 2514-2522.
40. Ferruzzi M, G., Blakeslee J. Digestion, absorption, and cancer preventative activity of dietary chlorophyll derivatives. *Nutrition Research* 2007; 27(1): 1-12.
41. Pangestuti R, Kim S-K. Biological activities and health benefit effects of natural pigments derived from marine algae. *Journal of Functional Foods* 2011; 3(4): 255-266.
42. Kong C-S, Kim J, Yoon N-Y, Kim S-K. Induction of apoptosis by phloroglucinol derivative from *Ecklonia Cava* in MCF-7 human breast cancer cells. *Food and Chemical Toxicology* 2009; 47(7): 1653-1658.

43. Gagez A-L, Thiery V, Pasquet V, Cadoret J-P, Picot L. Epoxycarotenoids and Cancer. Review. *Current Bioactive Compounds* 2012; 8(2): 109-141.
44. Kotake-Nara E, Asai A, Nagao A. Neoxanthin and fucoxanthin induce apoptosis in PC-3 human prostate cancer cells. *Cancer letters* 2005; 220(1): 75-84.
45. Liu Z, Xu P, Yu L, Zeng W. Microtubule-targeting Anticancer Agents from Marine Natural Source. *Anticancer Agents Med Chem* 2013; 7: 7.
46. Ishikawa C, Tafuku S, Kadekaru T, Sawada S, Tomita M, Okudaira T, Nakazato T, Toda T, Uchihara JN, Taira N. Antiadult T-cell leukemia effects of brown algae fucoxanthin and its deacetylated product, fucoxanthinol. *International journal of cancer* 2008; 123(11): 2702-2712.
47. Farooqi AA, Butt G, Razzaq Z. Algae extracts and methyl jasmonate anti-cancer activities in prostate cancer: choreographers of 'the dance macabre'. *Cancer Cell Int* 2012; 12(1): 50.
48. Farooqi AA, Butt G, Razzaq Z. Algae extracts and methyl jasmonate anti-cancer activities in prostate cancer: choreographers of 'the dance macabre'. *Cancer cell international* 2012; 12(1): 50.
49. Ale MT, Maruyama H, Tamauchi H, Mikkelsen JD, Meyer AS. Fucose-containing sulfated polysaccharides from brown seaweeds inhibit proliferation of melanoma cells and induce apoptosis by activation of caspase-3 *in vitro*. *Marine drugs* 2011; 9(12): 2605-2621.
50. Noda K, Tanaka K, Yamada A, Ogata J, Tanaka H, Shoyama Y. Simple assay for antitumour immunoactive glycoprotein derived from Chlorella vulgaris strain CK22 using ELISA. *Phytotherapy Research* 2002; 16(6): 581-585.
51. Ramos AL, Torello CO, Queiroz ML. Chlorella vulgaris modulates immuno-myelopoietic activity and enhances the resistance of tumor-bearing mice. *Nutrition and cancer* 2010; 62(8): 1170-1180.
52. Shin ES, Hwang HJ, Kim IH, Nam TJ. A glycoprotein from Porphyra yezoensis produces anti-inflammatory effects in liposaccharide-stimulated macrophages via the TLR4 signaling pathway. *Int J Mol Med* 2011; 28(5): 809-815.
53. Kim YM, Kim IH, Nam TJ. Induction of apoptosis signaling by glycoprotein of Capsosiphon fulvescens in human gastric cancer (AGS) cells. *Nutr Cancer* 2012; 64(5): 761-769.
54. Go H, Hwang HJ, Nam TJ. A glycoprotein from Laminaria japonica induces apoptosis in HT-29 colon cancer cells. *Toxicol In vitro* 2010; 24(6): 1546-1553.
55. Areche C, San-Martín A, Rovirosa J, Muñoz MA, Hernández-Barragán A, Bucio MA, Joseph-Nathan P. Stereostructure Reassignment and Absolute Configuration of Isoepitaondiol, a Meroditerpenoid from Stypopodium flabelliforme. *Journal of Natural Products* 2009; 73(1): 79-82.
56. Suárez Korsnes M, Espenes A. Yessotoxin as an apoptotic inducer. *Toxicon* 2011; 57(7): 947-958.
57. Pang M, Gao C-L, Wu Z-X, Lv N, Wang Z-L, Tang X-X, Qu P. Apoptosis induced by yessotoxins in hela human cervical cancer cells *in vitro*. *Molecular Medicine Reports* 2010; 3(4): 629-634.
58. Campos A, Souza CB, Lhullier C, Falkenberg M, Schenkel EP, Ribeiro do Valle RM, Siqueira JM. Anti tumour effects of elatol, a marine derivative compound obtained from red algae Laurencia microcladia. *Journal of Pharmacy and Pharmacology* 2012; 64(8): 1146-1154.
59. Liu M, Zhang W, Wei J, Qiu L, Lin X. Marine bromophenol bis (2, 3-dibromo-4, 5-dihydroxybenzyl) ether, induces mitochondrial apoptosis in K562 cells and inhibits topoisomerase I *in vitro*. *Toxicology letters* 2012; 211(2): 126-134.
60. Heo S-J, Kim K-N, Yoon W-J, Oh C, Choi Y-U, Affan A, Lee Y-J, Lee H-S, Kang D-H. Chromene induces apoptosis via caspase-3 activation in human leukemia HL-60 cells. *Food and Chemical Toxicology* 2011; 49(9): 1998-2004.
61. Shibata M, Shimura T, Nishina Y, Gonda K, Matsuo S, Abe H. PSK decreased FOLFOX4-induced peripheral neuropathy and bone marrow suppression in patients with metastatic colorectal cancer. *Gan To Kagaku Ryoho* 2011; 38: 797-801.

62. Guzman M. Cannabinoids: potential anticancer agents. *Nat Rev Cancer* 2003; 3(10): 745-755.
63. Whibley CE, McPhail KL, Keyzers RA, Maritz MF, Leaner VD, Birrer MJ, Davies-Coleman MT, Hendricks DT. Reactive oxygen species mediated apoptosis of esophageal cancer cells induced by marine triprenyl toluquinones and toluhydroquinones. *Mol Cancer Ther* 2007; 6(9): 2535-2543.
64. Jassbi AR, Zamanizadehnajari S, Baldwin IT. Phytotoxic volatiles in the roots and shoots of Artemisia tridentata as detected by headspace solid-phase microextraction and gas chromatographic-mass spectrometry analysis. *J Chem Ecol* 2010; 36: 1398-1407.
65. Kegge W, Pierik R. Biogenic volatile organic compounds and plant competition. *Trends Plant Sci* 2010; 15: 126-132.
66. de la Mare JA, Lawson JC, Chiwakata MT, Beukes DR, Edkins AL, Blatch GL. Quinones and halogenated monoterpenes of algal origin show anti-proliferative effects against breast cancer cells *in vitro*. *Invest New Drugs* 2012; 30(6): 2187-2200.
67. Afolayan AF, Mann MGA, Lategan CA, Smith PJ, Bolton JJ, Beukes DR. Antiplasmodial halogenated monoterpenes from the marine red alga Plocamium cornutum. *Phytochemistry* 2009; 70: 597-600.
68. Knott MG, Mkwananzi H, Arendse CE, Hendricks DT, Bolton JJ, Beukes DR. Plocoralides A-C, polyhalogenated monoterpenes from the marine alga *Plocamium corallorhiza*. *Phytochemistry* 2005; 66: 1108-1112.
69. Mann MGA, Mkwananzi HB, Antunes EM, Whibley CE, Hendricks DT, Bolton JJ, Beukes DR. Halogenated Monoterpene Aldehydes from the South African Marine Alga Plocamium corallorhiza. *Journal of Natural Products* 2007; 70 596-599.
70. de Ines C, Argandona VH, Rovirosa J, San-Martin A, Diaz-Marrero AR, Cueto M, Gonzalez-Coloma A. Cytotoxic activity of halogenated monoterpenes from *Plocamium cartilagineum*. *Verlag der Zeitschrift fur Naturforschung* 2004; 59: 339-344.
71. Lawson JC. Analysis of the anti-cancer activity of novel indigenous algal compounds in breast cancer: towards the development of a model for screening anti-cancer stem cell activity: Rhodes University; 2010.
72. D'Orazio N, Gammone MA, Gemello E, De Girolamo M, Cusenza S, Riccioni G. Marine bioactives: Pharmacological properties and potential applications against inflammatory diseases. *Marine drugs* 2012; 10(4): 812-833.
73. Ganesan P, Noda K, Manabe Y, Ohkubo T, Tanaka Y, Maoka T, Sugawara T, Hirata T. Siphonaxanthin, a marine carotenoid from green algae, effectively induces apoptosis in human leukemia (HL-60) cells. *Biochimica et biophysica acta* 2011; 1810(5): 497-503.
74. Yuan YV, Walsh NA. Antioxidant and antiproliferative activities of extracts from a variety of edible seaweeds. *Food Chem Toxicol* 2006; 44(7): 1144-1150.
75. Sousa C, Valev D, Vermue MH, Wijffels RH. Effect of dynamic oxygen concentrations on the growth of Neochloris oleoabundans at sub-saturating light conditions. *Bioresource technology* 2013; 142C: 95-100.
76. Sparidans RW, Stokvis E, Jimeno JM, Lopez-Lazaro L, Schellens JH, Beijnen JH. Chemical and enzymatic stability of a cyclic depsipeptide, the novel, marine-derived, anti-cancer agent kahalalide F. *Anticancer Drugs* 2001; 12(7): 575-582.
77. Knott MG, Mkwananzi H, Arendse CE, Hendricks DT, Bolton JJ, Beukes DR. Plocoralides A–C, polyhalogenated monoterpenes from the marine alga< i> Plocamium corallorhiza</i>. *Phytochemistry* 2005; 66(10): 1108-1112.
78. Mann MG, Mkwananzi HB, Antunes EM, Whibley CE, Hendricks DT, Bolton JJ, Beukes DR. Halogenated monoterpene aldehydes from the South African marine alga Plocamium corallorhiza. *Journal of Natural Products* 2007; 70(4): 596-599.
79. de la Mare JA, Sterrenberg JN, Sukhthankar MG, Chiwakata MT, Beukes DR, Blatch GL, Edkins AL. Assessment of potential anti-cancer stem cell activity of marine algal compounds using an *in vitro* mammosphere assay. *Cancer Cell Int* 2013; 13(1): 1475-2867.
80. Afolayan AF, Bolton JJ, Lategan CA, Smith PJ, Beukes DR. Fucoxanthin, tetraprenylated toluquinone and toluhydroquinone metabolites from Sargassum heterophyllum

inhibit the *in vitro* growth of the malaria parasite Plasmodium falciparum. *Zeitschrift für Naturforschung C, A journal of biosciences* 2008; 63(11): 848.
81. Terasaki M, Asai A, Zhang H, Nagao A. A highly polar xanthophyll of 9′-cis-neoxanthin induces apoptosis in HCT116 human colon cancer cells through mitochondrial dysfunction. *Molecular and cellular biochemistry* 2007; 300(1-2): 227-237.
82. Subbaraju GV, Golakoti T, Patterson GM, Moore RE. Three new cryptophycins from Nostoc sp. GSV 224. *J Nat Prod* 1997; 60(3): 302-305.
83. Barbier G, Oesterhelt C, Larson MD, Halgren RG, Wilkerson C, Garavito RM, Benning C, Weber AP. Comparative genomics of two closely related unicellular thermo-acidophilic red algae, Galdieria sulphuraria and Cyanidioschyzon merolae, reveals the molecular basis of the metabolic flexibility of Galdieria sulphuraria and significant differences in carbohydrate metabolism of both algae. *Plant physiology* 2005; 137(2): 460-474.
84. Religa P, Kazi M, Thyberg J, Gaciong Z, Swedenborg J, Hedin U. Fucoidan inhibits smooth muscle cell proliferation and reduces mitogen-activated protein kinase activity. *European Journal of Vascular and Endovascular Surgery* 2000; 20(5): 419-426.
85. Singh RK, Tiwari SP, Rai AK, Mohapatra TM. Cyanobacteria: an emerging source for drug discovery. *The Journal of antibiotics* 2011; 64(6): 401-412.

Table 1. Algae-derived natural anticancer extracts[41,79,72]

S. No.	Extracts	Source	References
1	Siphonaxanthin	*Codium fragile*	73
2	Kappa-carrageenan	*Kappaphycus striatum*	74
3	Alginate	*Sargassum vulgare*	75
4	Kahalalide F	*Bryopsis sp.*	76
5	Plocoralide A/B/C/D/E	*Plocamium corallorhiza*	77,78
6	Plocoral A/B	*Plocamium corallorhiza*	71,79
7	Sargaquinoic Acid	*Sargassum heterophyllum*	80
8	Plocornulide A	*Plocamium cornutum*	79
9	Plocornulide C-erythro	*Plocamium cornutum*	79
10	Plocornulide C-threo	*Plocamium cornutum*	79
11	Fucoxanthin	*Undaria pinnatifida*	81
12	Apratoxins	Cyanobacteria	11
13	Cyptophycin 1	*Nostoc linckia*	82
14	Caulerpenyne	*Caulerpa sp.*	83
15	Fucoidan	Ascophyllum nodosum	84
16	Phycocyanin	*Spirulina sp.*	85