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ARTICLE

Biochemical Composition and Anticancer Effect of Different Seaweed Species (*In-vitro and In-vivo* Studies)

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ABSTRACT

Seaweed is an enormous resource comprised with natural bioactive compounds with several therapeutic effects including anticancer activity. In this context, the biochemical composition of seaweed plays a major role. Many biochemical compounds isolated from seaweed, fractions of seaweed and crude extracts has revealed ability of seaweed to fight against several cancer types. In this contrast seaweed extracts inhibit cancer cell growth and proliferation by inducing apoptosis and by inhibiting metastasis activity. In this review, biochemical and anticancer properties of seaweeds are discussed and this will provide the basic information to develop a novel chemotherapeutic drug to challenge the cancers.

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1. Introduction

Cancer is a dreadful disease causes due to uncontrolled cell proliferation and migration [17,26]. Among all human cancer types, lung cancer and colorectal cancer are the major cancers found in male whereas breast cancer, cervical cancer and lung cancer are considered as the common cancers found in female [1,40]. Although chemotherapy and radiotherapy treatments are practiced to cure cancers, the survival rate is still low and many side effects are also reported [23]. Due to the continuing of failure of the availability of effective chemo-preventive agents for cancers, therapeutic agents from biological resources are being experimented to control this malignant disease [8,11,18]. Seaweeds are marine macro algae, found in intertidal and sub-tidal zones and classified based on their pigmentation and chemical composition as Chlorophyta (green algae), Rhodophyta (red algae) and Phaeophyta (brown algae) [6,23]. *Laminaria* sp., *Fucus* sp., *Ascophyllum* sp., *Porphyra* sp., *Ulva* sp., *Sargassum* sp. and *Gracilaria* sp. are some of the examples for the famous edible seaweed species that comprise with many bioactive compounds coming under the groups of polysaccharides, proteins, lipids, minerals and vitamins [14,1]. Moreover, due the availability of theses bioactive compounds many seaweed species account for promising health promoting effects such as antibacterial, antiviral, anti-inflammatory, antiulcer and anticancer activities [1,13,33,41]. Therefore some secondary metabolites in seaweeds are extracted and incorporated into several products such as foods, medicines and cosmetics [5]. Recently, seaweeds are increasingly being considered as a source with effective anticancer agents that are able to lower the risk of cancer [1,17,26]. In this context, investigation of anticancer drugs with less or no side effects has become an interesting topic in novel research field [37,43].

2. Biochemical Composition of Seaweeds

There are two types of biochemical substances present in seaweeds as high molecular materials and low molecular materials. High molecular materials such as dietary fibres are not absorbed into the human body whereas low molecular materials are absorbed directly [14]. Though seaweeds comprise with several biochemical compounds including carbohydrates, proteins, lipids, vitamins, polyphenols, free amino acids and minerals [7,14,24] the composition varies based on the geographical location, seasonal variation and water temperature [14,24].

Seaweeds contain 20% - 76% (dry weight) of polysaccharides as structural and storage compounds. Cellulose, starch, hemicellulose, fucoidan, alginic acids, Sulfated fucans, alginate and laminarin are the polysaccharides which are mainly present in the seaweeds that provide strength and flexibility to the cell wall [5,13,14]. Out of three seaweed types red seaweeds consist with the highest protein content which accounts for 30%-40% of dry weight whereas brown seaweeds contain 15% and green seaweeds contain 30% of dry weight [34]. Many essential amino acids, such as glycine, alanine, arginine and glutamic acids are present in seaweeds. However, the lipid content of seaweeds is comparatively low (1%-5% of dry weight) and it contains a high proportion of essential fatty acids and poly unsaturated fatty acids such as ω-3 and ω-6 [30]. Vitamin B, C, A and D are the most common vitamins present in the seaweeds. In general, seaweeds accounts for 36% (dry weight) of minerals including, potassium, sodium, magnesium, calcium, sulfur, chlorine, phosphorus, iron, zinc, iodine, copper and some other trace metals [34]. Several studies reported that there are severel types of secondary metabolities with therapeutic effect are present in seaweeds (Table 1)

Table 1. Secondary metabolites in seaweeds

Family	Seaweed Species	Secondary Metabolites	Reference
Pheophyta	*Fucus vesiculosus* *Fucus evanescens* *Ascophyllum nodosum* *Undaria pinnatifida* *Sargassum thunbergii* *Ecklonia cava*	Fucoidan	[3,13,16, 20,32,39,45]
	Laminaria sp.	Laminarin	[13,31]
	Sargassum heterophyllum *Laminaria ochotensis* *Hijikia fusiformis* *Undaria pinnatifida* *Ectocarpus siliculosus*	Fucoxanthin	[2, 25, 38]
Chlorophyta	*Nitella Hookeri* *Ulva fasciata*	Flavonoids	[31]
	Laurencia glandulifera	Dactylone	[10]

3. Anticancer Effect of Seaweeds

Uncontrolled cell growth and proliferation is the main reason for cancer formation. Chemo-preventive agents extracted from natural resources have got the attention due to the ability to suppress cancer cell formation with lesser or no side effects with compared to available chemotherapeutic agents [20]. Basically, cell death can be caused by any chemotherapeutic agent through the cell

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cycle arrest by targeting necrotic pathway or apoptotic pathway of respective cells [23,26]. Bioactive compounds are able to induce apoptosis in cancer cells, this is one of the key mechanisms in cancer therapy because apoptosis is a kind of programmed cell death which can kill only the targeting cancer cells without causing damage to normal surrounding cells [2,40]. In this context, cell death is evoked through intrinsic mitochondrial pathway or extrinsic death receptor pathway [23,40]. Several studies have proven that seaweed constitute many novel bioactive compounds with anticancer effect and able to induce apoptosis in several types of cancer cells [1,3,9,13,35,37].

Anticancer effect of methanolic extract of *Caulerpa racemosa* mentioned was examined against HL-60 (Human promyelocytic leukemia) cell line and a remarkable cell growth inhibition was reported by Lakmal, *et al.*, 2014 [21] in dose - dependent manner with compared to normal cell line; vero (Monkey kidney cell line). Apoptotic body formation and DNA damage of treated HL-60 cancer cells were obsereved under fluorescent microscopy and flow cytometric analysis was also showed dose dependent sub-G1 DNA accumulation in HL-60 cell line. Aqueous and methanolic extract *Kappaphycus striatum* has showed cell growth inhibition activity against HeLa (Cervical adenocarcinoma) cell line and this study explains that the molecular weight, monosaccharide sequence, bond formation and charge of molecules are the characteristics of bioactive compounds present in seaweed extracts which support seaweeds to act as an anticancer agent [22]. Zandi, *et al.*, 2010 [42] has found that the aqueous extract of *Sargassum oligocystum* shows cytotoxic activity on K562 (Human chronic myelogenous leukemia) and Human Daudi (Burkitt Lymphoma) cell lines in dose dependet manner. Moreover by another study Zandi, *et al.*, 2010 [43] expalins that the aqueous extract of *Gracilaria corticata* filtered with Whatman paper No.1 filter paper showed more pormising cell growth inhibition results on Jurkat and Molt-4 (Human lymphoblast) cell lines and they emphasis that filtration is the one of the best methods of sterilising the seaweed extarcts since some of the bioactive compounds in seaweeds are heat sensitive. MCF 7 (Human breast adenocarcinoma) cell line treated with aqueous extracts of different seaweed species such as *Gracillaria corticata, Ulva fasiata, Chaetomorpha antennina* showed growth inhibitory effect and morphological observation such as cell shrinkage and cell shape changes related to apoptotic induction were also observed [4].

Methanolic extract of *Sargassum muticum* has showed antiproliferative activity by inducing apoptosis in MCF-7 (Human breast adenocarcinoma) cell line. Electron microscopic images with membrane blebbing, apoptotic body formation and microvilli reduction, the morphological changes of treated cells stained with Hoechst 33342 and flow cytometric analysis indicating the accumulation of treated cells at sub-G1 phase provide evidence on inducing apoptosis by Methanolic extract of *Sargassum muticum* [28]. MCF-7 (Human breast cancer cell line) and HepG2 (Human liver cancer cell line) treated with methanolic extracts of *Enteromorpha antenna, Gracilaria corticata* and *Enteromorpha linza* has shown cytotoxic activity with compared to normal Vero cell line (Monkey kidney cell line) [29]. Gomes, *et al*., 2015 [12] found the Methanolic extracts of *Dictyota cilliolata* and *Dictyota menstrualis* shows dose-dependent and time-dependent antiprolifertive effect on HeLa (Human cervical cancer cell line). Nuclear morphology changes such as formation of apoptotic bodies and chromatin condensation in the cells stained with 4, 6-Diamidino-2-phenylindole (DAPI) staining was observed under fluorescent microscope. It is reported that percentage of annexin-positive (annexin V-FITC+/ PI−) cells Flow was increased and it is a sign of early apoptosis process of cells. Further the results highlighted that the methanolic extracts of *Dictyota cilliolata* inhibits the growth of HeLa cells by blocking the cell cycle at the S phase whereas *Dictyota menstrualis* shows apoptotic induction without inducing cell cycle arrest. Caspase 3 and Caspase 9 activation empahasis that intrinsic apoptotic induction occurs by the seaweed extracts in the cancer cells. Ethanol extract of *Ulva fasciata* has showed growth inhibition due to apoptosis induction HCT 116 (Human colon cancer) through mitochondrial pathway by increasing cell at sub-G1 phase and activation of Caspase 3 and Caspase 9 [36].

Fractions of polysaccharides; SP-3-1 and SP-3-2 extracted from *Sargassum pallidum* were treated on HepG2 (human hepatoma), A549 (human lung cancer) and MGC-803 (Human gastric cancer) cell lines and evaluated by MTT assay. SP-3 fraction with the highest sulfate content exhibited higher antitumor activity against all tested cancer cell lines. Further, this study states structure, glycosidic linkages and sequence of monosaccharaides effects on the function of the extracted polysaccharides [41]. Anticancer effect of a sterol fraction of *Porphyra dentata* was evaluated against 4T1 breast cancer cell line and pronounced in dose dependent and time dependent cell proliferation inhibition of was resulted in the treated 4T1 cells and percentage of apoptotic-necrotic cells increased was also increased due to the results of PI and annexin V dual staining [19]. Liu *et al.* (2016) [23] evaluted the anticancer effect of a

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Table 2. Anticancer activity of different seaweed extracts

Extract type	Seaweed Species	Cancer cell type	*In-vitro* analysis				References
			MTT Assay	Morphological chances	Cell cycle arrest	Gene expression	
Methanoic	*Caulerpa racemosa*	HL-60 (Human promyelocytic leukemia)	+	+	+		[21]
	Sargassum muticum	MCF-7 (Human breast adenocarcinoma)	+	+	+		[28]
	Enteromorpha antenna *Enteromorpha linza*	MCF-7 (Human breast cancer cell line) HepG2 (Human liver cancer cell line)	+				[29]
	Gracilaria corticata	MCF-7 (Human breast cancer cell line) HepG2 (Human liver cancer cell line)	+				[29]
	Dictyota cilliolata *Dictyota menstrualis*	HeLa (Human cervical cancer cell line)	+	+	+	Caspase 3 Caspase 9	[12]
Aqueous	*Sargassum oligocystum*	K562 (Human chronic myelogenous leukemia) Daudi (Human Burkitt lymphoma)	+				[43]
	Gracilaria corticata	Jurkat (Human lymphoblast) Molt-4 (Human lymphoblast) MCF-7 (Human breast adenocarcinoma)	+				[4,42]
	Ulva fasiata	MCF-7 (Human breast adenocarcinoma)	+				[4]
	Chaetomorpha antennina	MCF-7 (Human breast adenocarcinoma)	+				[4]
Ethanol	*Ulva fasciata*	HCT 116 (Human colon cancer)	+	+	+	Caspase 3 Caspase 9	[36]

novel Sulfated Polysaccharides (SPS), extracted from *Sargassum integerrimum* against A549 (Human lung cancer) cell line. Cell growth inhibition was resulted due to necrosis or apoptosis the treated and control cells were stained using Hoechst 33258 staining and morphological changes were observed. Comparatively, typical apoptotic cell characteristics such as cell shrinkage, cell bubbling, fragment shape nucleus and nuclear shrinkage were observed in the SPS treated cells. Flow cytometric analysis using Annexin V-FITC/PI double staining and JC-1 staining also confirms that the growth inhibition is due to apoptosis induction and further due to loss of mitochondrial membrane potential. Moreover, anti-apoptotic and pro-apoptotic protein markers expression were also tested using western blotting. According to the results, the expression level of P53; tumor suppressor protein was increased and Bcl-2; anti-apoptotic protein expression was down regulated whereas Bax; pro-apoptotic gene expression was decreased.

Several studies have found that fucoidan extracted from different seaweed species as natural bioactive compound with anticancer effect (Table 2). Fucoidan is a type of sulphated polysaccharide mainly present in brown seaweeds. There are many studies to evident the induction of apoptosis in human colon cancer cell lines such as HCT-15, WiDr, HCT116 and HT-29 by fucoidan [16,17,20]. Moreover HCT-15 cells treated with fucoidan inhibited the growth of colon cancer cell lines in dose dependent manner through apoptosis induction. The treated cells have been visualized with condensed and fragmented nucleus and Bcl-2 expression was down regulated whereas Bax, Pro-caspase 3 and 9 expressions were up regulated by the fucoidan treated cells there for it proves that this growth inhibition is due to apoptosis induction

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in the colon cancer cell lines by fucoidan [16]. Further, HCT116 and HT-29, human colon cancer cell lines treated with fucoidan (5-20 µg/ml concentrations) have also showed remarkable dose dependent and time dependent cell growth inhibition and any significant cytotoxic effect was not reported on FHC (human normal colon epithelial) cell line. This growth inhibition was also due to apoptosis induction via activation of Caspase 3, 7, 8 and 9 [20].

Table 3. Anticancer activity of bioactive compounds isolated from seaweeds

Bioactive compound	Seaweed species used to extract Fucoidan	Cancer cell type	Reference
Fucoidan	*Fucus vesiculosus*	HCT-15 (Human colon carcinoma cells)	[16]
		HT-29 (Human colon adenocarcinoma) HCT116 (Human colon adenocarcinoma)	[20]
	Sargassum sp. *Turbinaria* sp. *Padina* sp.	WiDr (Human colon adenocarcinoma) MCF-7 (Human breast adenocarcinoma)	[17]
	Sargassum oligocystum	Daudi (Burkitt lymphoma cells) K562 (Human chronic myelogenous)	[42]
	Caulerpa racemosa	HL-60 (Human promyelocytic leukemia cell line)	[21]
Laminarin	*Laminaria digitata*	HT-29 (Human colon adenocarcinoma)	[31]
Fucaxanthin	*Laminaria japonica*	EJ-1(Human bladder cancers)	[44]
	Undaria pinnatifida	HL-60 (Human promyelocytic leukemia cell line)	[15]

Laminarin is another bioacive compound present in seaweeds examined for anticancer properties. Laminarin extracted from *Laminaria digitata* has shown anticancer effects against HT-29 colon cancer cell. Laminarin showed an activity against HT-29 cell line in a dose-dependent manner. Accumulation of sub-G1 and G2-M during the flow cytometric analysis and inhibition of phosphorylation and ErbB2 expression reveals that Laminarin induces apoptosis through ErbB signaling pathway [31].

Anticancer effect of fucoxanthin extracted from *Laminaria japonica* was tested against EJ-1(Human bladder cancers) cancer cell line and observed time and dose dependent cell viability reduction. Cell morpholgical changes observed by contrastand fluorescence microscope and activetion of caspase-3 reveals that this cell viability reduction is due to apoptosis induction [44]. Fucoxanthin extracted from *Undaria pinnatifida* inhbited HL-60 (Human promyelocytic leukemia) cell line proliferation due to apoptosis induction. The results such as DNA fragmentation resuted from agarose gel electrophoresis and sandwich ELISA tests prove the activity of fucoxanthin against Leukemia cancer cell line [15].

Further, not only *in-vitro* studies but also *in-vivo* studies provide the evidance of anticancer activity of seaweeds. In this contrast, LLC (Lewis Lung Carcinoma) cells were transplanted in C57BL/6 mice and treatments (fucoidan and cyclophosphamide) were started after nine days of transplantation. it is recorded that fucoidan shows and atiancer and antimetastatic activity when the drug is used combined with cyclophosphamide [4]. Abirami & Kowsalya, 2012 [1] investigated anticancer effect of *Ulva fasciata* using albino mice (*in-vivo*). DAL (Dalton's Ascites Lymphoma) cells were transplanted in swiss albino mice and treated with methanolic extract and aqueous extracts of *Ulva fasciata* once daily for 14 days. The parameters such as hematological parameters, lipid profile, liver function tests, body weight, cancer cell counts were examined and methanolic and aqueous exracts of *Ulva fasciata* showed *in-vivo* anticancer effect against DAL cancer type. Further mammary cancer induced female rats were treated with *Eucheuma cottonii* extract (150 and 300 mg/kg of body weight) for four weeks. The tumor was reduced by E. *cottonii* extract and inhibition rate showed dose-dependent variation [27].

4. Conclusion

The therapeutic effect of seaweeds was explored due the presence of novel bioactive compounds. In this context anticancer effect of seaweed plays a major role by inducing apoptosis through intrinsic and extrinsic pathways [12,20]. Seaweed are comprised with many secondary metabolities and some of them have been isolated and further studies are reqiuired for isolation of other theraeutic compounds from seaweeds since the most of them show cytotoxic activity against cancre cells and not in normal cells. Thus further studies will open the gate to reveal new chemotherapeutic agents which are able to fight against cancers while having no or less impact on normal cells.

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