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Review Article

BIOCHEMICAL COMPOSITION OF SEAWEEDS AND THEIR ANTI-CANCER PROPERTIES AGAINST HUMAN PAPILLOMAVIRUS (HPV) – A REVIEW

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ABSTRACT

Seaweeds were traditionally used as food stuff in Asian countries for centuries, as early as 2700 BC. Most recently seaweeds have been utilized in Japan as raw materials in the manufacture of many seaweed food products such as jam, cheese, wine, tea, soup and noodles. Seaweeds are highly nutritive foods containing proteins, vitamins, minerals, fiber contents and essential fatty acids. Seaweeds have become a valuable vegetable (fresh or dried) and an important food ingredient in the human diet. Seaweeds constitute some of the most important reservoirs of new therapeutic compounds for humans. Several of them have been shown to have many biological activities, including anticancer activity. Marine algae- derived products play an important role in preventing inflammatory reactions and carcinogenesis by modulating the effects of oxidative stress.

Keywords: Seaweeds, HPV, carbohydrates, proteins, lipids, minerals, vitamins.

INTRODUCTION

Cancer of the cervix uteri is the 4th most common cancer among worldwide with an estimated 527,624 new cases and ranks as the 2nd cause of female cancer in India with 265,653 deaths in 2012 and 122,844 new cervical cancer cases diagnosed annually in India[1] . Virtually 100% of cervical tumors are attributable to HPV infection which is annually generating 530,000 cervical cancer cases worldwide[2,3]. There are highly effective prophylactic HPV vaccines for HPV infection which are publicly available for preventing the transmission of HPV in the developed countries.

However, there are certain drawbacks for these vaccines that they are relatively expensive and are likely to be Papillomavirus restricted in their protection[4]. Thus, these vaccines may not be affordable and initially not available to women in all parts of the world. Further, they may not offer protection against all cancers associated with different HPV types. Therefore, the urge in search for potential drug candidates against various HPV strains which has higher inhibitory activities is increasing in the pharmaceutical industry. With this regard, natural bioactive compounds derived from marine sources are found to have great sources for the development of new generation anti-HPV therapeutics, which is more effective with a fewer side effects. Among which Seaweeds or marine algae constitute one of the commercially important renewable marine living resources. Seaweeds have been an important dietary component since, at least fourth century in Japan and sixth century in China. In Korea, consumption of seaweeds is a common practice[5].

Based on their pigmentation, seaweeds are classified into Chlorophyta (Green algae), Rhodophyta (Red algae) and Phaeophyta (Brown algae). Seaweeds such as *Caulerpa, Ulva, Enteromorpha, Codium* and *Monostroma* (Green algae; Figure 1); *Sargassum, Hydroclalhrus, Padina, Macrocystis* (Brown algae; Figure 2); *Porphyra, Gracilaria, Eucheuma, Laurencia* and *Acanthophora* (Red algae; Figure 3) are used for human consumption in the form of soup, salad, curry which are protein rich. Marine algae are also used in different parts of the world as animal feed and fertilizer, they contain more than 60 trace elements, carbohydrate, iodine, bromine, vitamins and some bioactive substances[6].

Certain seaweeds 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[7]. Fucoidan isolated from brown seaweed such as *Undaria* and *Laminaria* showed anticoagulant, antiviral and anticancer properties[8,9]. Seaweeds have become a valuable vegetable (fresh or dried) and an important food ingredient in the human diet[10].

Several studies have reported that compounds extracted from seaweed may be effective anticancer agents. This review will mainly focus on the biochemical compounds present in marine organisms and the importance of seaweed, their potential as therapeutic application against cervical cancer.

Biochemical composition of seaweeds

The protein, carbohydrate and organic carbon content was estimated in 43 marine algal species collected from different marine stations along the Maharashtra coast among which more protein and carbohydrate content was recorded in Chlorophycean , Rhodophycean and Phaeophycean algae by Dhargalkar *et al*.,[11].

Chakraborthy and Santra recorded higher carbohydrate in the green seaweeds *U. lactuca* (35.27%) and *Enteromorpha intestinalis* (30.58%)[12]. The carbohydrate content of sea weed collected from Mandapam coast varied from 20.47 to 23.9% and maximum carbohydrate concentration was recorded from brown algae *Turbinaria conoides* (23.9%), *S. tenerimum* (23.55%), *S. wightii* (23.50%), followed by the green alga *E.intestinalis* (23.84%), and red algae *Hypnea valentiae*(23.60%), *Acanthophora spicifera* (23.54%). While the minimum carbohydrate content was reported from green alga *Codium tomentosum*(20.47%) followed by brown algae *Padina gymnospora* (21.88%), *Colpomenia sinuosa* (22.46%) and the red alga *G. folifera* (22.32%)[13].

Fifty individual plants of *Saccharina, Fucus (serratus and spiralis)* and *Ascophyllum* were recorded for glucose content and were found to have 65%, 30% and 20% of the total sugars in an autumn sample respectively[14]. The study percentage of *Hypnea valentiae for* carbohydrate content was higher than those of several seaweed species of the red algae genus *Hypnea* collected in Darwin Harbour[15].

Concentration of total polysaccharides in the seaweed species of interest, range from 4% to 76% of their dry weight; among which highest contents are found in species such as *Ascophyllum, Porphyra and Palmaria* (Table1). Green seaweed species such as *Ulva* also have a high polysaccharide content, up to 65% of dry weight. Arasaki and Arasaki observed seaweeds for their richness in polysaccharides, minerals and certain vitamins[16].

Brown alga *Tubinaria ornata* from Gulf of Mannar region was observed for highest protein content by Dinesh *et al*.,[17]. Mairh *et al*.,[18] reported 22.22% of crude protein in *Ulva fasciata*, which is frequently consumed under the name of ``ao-nori'' by the Japanese people, was observed for high protein level between 20 and 26% (dry product)[19]. Red seaweeds such as *Porphyra tenera* (47% of dry mass) or *Palmaria palmata* (35% of dry mass) were recorded higher protein levels (Table 2)[20].

The major metabolites such as proteins, carbohydrates and lipids were estimated by Dhargalkar[21]. Red algae (Rhodophyceae) were collected from Mandapam coastal regions southeast coast of India for proximate composition evaluation and the protein content varied from 3.25±0.36 to 17.08±0.28%; maximum protein was recorded in *P. gymnospora* (17.08±0.28%) followed by *E. intestinalis* (16.38±0.50%) and *S. tenerimum*(12.42±0.63%).

Munda reported that in *Fucus* sp. (brown seaweeds), aspartic and glutamic acids can represent between 22 and 44% of the total amino acids[22]. Marine macro algae varieties contained low amount of lipids; they are the sources of poly unsaturated fatty acids (PUFA). The distribution of fatty acid in seaweed products showed high level of omega-3 fatty acids and demonstrated a nutritionally ideal omega-6/omega-3 free fatty acid ratio. Seaweeds contain up to 2% of dry weight of lipids and much of this lipid content is made up of polyunsaturated fatty acids[23,24].

The lipid content of seaweeds varied from 1.33 to 4.6; in that the maximum lipid content was observed in *Enteromorpha clathrata* (4.6%; Figure 1) followed by *G. folifera* (3.23%), *Codium tomentosum* (2.53%), *C. sinuosa* (2.337%) and *S. wightii* (2.337%). The minimum lipid concentration was observed in *E. intestinalis* (1.33%) followed by *P. gymnospora* (1.4%), *S. tenerimum* (1.46%) and *U. lactuca* (1.6%)[13]. In Japan, the lipid content of *P. gymnospora* products was exhibited: Biochemical and nutritional aspects (1.4±0.30%), *S. tenerimum* (1.46±0.20%) and *U. lactuca* (1.6±0.17%) values were smaller than those obtained for most of the seaweeds, which range from 2.80±0.23% to 3.49±0.28 %. This value which is relatively low; is comparable to results obtained from previous studies[25]. The higher result for carbohydrate content (64.00% dry weight.) in *Caulerpa lentillifera* was reported by Nguyen *et al*.[26].

Seaweeds are a well-known source of minerals. An adequate intake of minerals is required for a high nutritional quality of the diet which can help prevention of chronic nutrition-related diseases and degenerative diseases including cancer, cardiovascular disease, Alzheimer´s disease, and premature aging[27,28]. Seaweeds are considered as a potential material for the production of different nutraceuticals and food supplements[29,30]. The selected micro nutrients (Fe^+ Zn^+ Mn^+ Cu^+) of *Panax vietnamensis* were found to be higher (45.5– 309 mg/100 g dry weight) than any of the land vegetables as well as edible seaweeds like *C. lentillifera, Enteromorpha flexuosa, Monostroma oxysperum, Eucheuma denticulatum* and *Gracilaria parvispora* reported from Hawaii[31].

The mineral content of certain seaweeds was recorded higher than that of land plants and animal products[32]. Copper is present at a high level in seaweeds[33]. Daily intake of 8g of 'Kombu', as used in Asian cooking, contains 65% of the RNI for magnesium[34]. Seaweeds arre described as an ideal food-safe natural source of the mineral[35]. It is found that 8 g of *Porphyra umbilicalis* (Nori) provides 9 mg of vitamin C, or 15% of the RNI[36]. *U. lactuca* can provide vitamin B12 in excess of the recommended dietary allowances for Ireland of 1.4 g/day with 5g in 8g of dry foodstuff [37]. Seaweeds are known as an excellent source of vitamins and minerals[38]. Chapman and Chapman reported that 100 g of seaweed provides more than the daily requirement of Vitamin A, B2 and B12 and two thirds of the Vitamin C requirement (Table 3)[39].

Role of seaweeds in cervical cancer

The vital role of HPV16 in carcinogenesis was considered[40,41]. Thus most of the efforts for developing therapeutic HPV vaccines has been directed towards development of vaccines against HPV16 viral oncogenes *E6* and *E7*[42,43]. Though there is still no FDA approved anti-HPV drug listed so far, some Interferons (IFNs) are the only antiviral drugs approved for the therapy of benign HPV related lesions. Chinese medicine *chaihu* possesses good anti-HPV activities; it has inhibitory effects by interfering with the expression of HPV-DNA in genital warts[44].

Brown seaweed with low molecular weight fucoidan, mediated the broad-spectrum growth inhibition of human carcinoma cells, including HeLa cervix adenocarcinoma, HT1080 fibrosarcoma, K562 leukemia, U937 lymphoma, A549 lung adenocarcinoma and HL-60[45]. Fucoidan produced from brown algae was reported to inhibit HPV pesudovirus infection *in vitro* with the IC50 value of 1.1 μg/mL[46]. Brown algae could be a relevant source of anticancer compound[47]. Heterofucans from *Sargassum filipendula* exhibited anti-proliferative effects on cervical cells[48]. Fucoxanthin has been shown to induce apoptosis in human cervical cancer HeLa cells[49,50].

Marine polysaccharide carrageenan was able to generate antigen-specific immune responses and anti-tumor effects in female (C57BL/6) mice vaccinated with HPV16 E7 peptide vaccine[51]. Brown seaweeds were isolated for active sulfated homo-heterofucans which have shown effective antitumor activities with a wide range of mechanisms which stands as valuable source[52]. Sulfated polysaccharides, such as heparin, cellulose sulfate and dextran sulfate, were reported to block the infectivity of papillomaviruses[53]. Polysaccharide fraction SF isolated from the brown seaweed *Sargassum stenophyllum* with major fucose was reported to promote morphological modifications in HeLa cells at low (2.5μg/mL) concentrations[54]. Polysaccharides and terpenoids from brown algae are considered as promising bioactive molecules with anticancer activity by Taskin *et al.*[55],Devery *et al.,*[56].Polysaccharide-rich extract from *Sargassum filipendula, C. Agardh* showed anti-proliferative effect on HeLa cell (human uterine adenocarcinoma cell) proliferation(Table 4)[57].

Several heparan sulfate proteoglycans (HSPGs) serve as a primary receptor protein in natural HPV infection of keratinocytes as HPV receptors and support a putative role for syndecan[58]. Marine heparinoid polysaccharides such as alginic acid and fucoidan were reported to effectively block HPV pseudovirion infection just like heparin[59].

Carrageenans from marine sources were observed to inhibit HPV infection*.* Gliotoxin isolated from marine fungus *Aspergillus* sp. was found to induce apoptosis in HPV related cancer cells via the mitochondrial pathway leading to cell death[60]. Marine algae are important sources of non-animal sulfated polysaccharides and these biomolecules are widely studied on therapeutic applications such as anti-thrombotic, anticoagulant, antioxidant, anti-inflammatory and anti-proliferative compounds [61-64].

CONCLUSION

Edible seaweeds have been shown to be high in essential vitamins and minerals that would inflate a balanced diet if consumed regularly. Marine algae are known for natural richness in minerals, vitamins, polyunsaturated fatty acids and their low content lipids as well as high content of bioactive molecules. They can serve as good source of healthy food. Also seaweeds may solve the problems of deficiency of protein, carbohydrate and mineral deficiency in human nutrition by consuming them in daily life. Further seaweed will lead as a novel candidate in pharmaceuticals to develop a natural compound as an anticancer agent for production of potential anticancer drug and it is necessary to revitalize the use of seaweed in the newly health-conscious consumer environments of several countries.

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CONFLICTS OF INTEREST
No conflict of interest.

Fig. 1: ***Enteromorpha clathrata*** **(Green algae)**

Fig. 2: ***Padina boerengsnii*** **(Brown algae)**

Fig. 3: ***Gracilaria Spp*** **(Red algae)**

Table 1: Seaweed carbohydrate content by 8 g portion compared with guideline daily amounts (GDA) of fiber

Seaweed	Total fiber*	Soluble fiber*	Insoluble fiber*	Carbohydrates*	Fiber as % GDA†
Ascophyllum nodosum	2.8	2.4	0.4	4.2	11.6
Laminaria digitata	3.0	2.6	0.4	4.8	12.5
Himanthalia elongate	2.6	2.1	0.6	4.0	10.8
Undaria pinnatifida	2.8	2.4	0.4	3.9	11.6
Porphyra umbilicalis	2.7	2.1	0.7	3.8	11.25
Palmaria palmata	2.7	1.5	1.2	5.3	11.25
Ulva spp.	3.0	1.7	1.3	3.3	12.5
Enteromorpha spp.	3.0	1.8	1.3	4.8	12.5

*Values from the Institut de Phytonutrition (2004).[34]
†Guideline daily amounts from the Institute of Grocery Distribution (2006).[68]

Table 2: Composition of amino acids of some seaweeds (in g amino acid/100 g protein)

Amino acids	*Ulva armoricana*[10] (green seaweed)	*Ulva Pertusa*[19] (green seaweed)	*Palmaria palmata*[69] (red seaweed)	*Porphyra tenra*[19] (red seaweed)
Histidine	1.2±2.1	4.0	0.5±1.2	1.4
Isoleucine	2.3±3.6	3.5	3.5±3.7	4.0
Leucine	4.6±6.7	6.9	5.9±7.1	8.7
Lysine	3.5±4.4	4.5	2.7±5.0	4.5
Methionine	1.4±2.6	1.6	2.7±4.5	1.1
Phenylalanine	5.0±7.1	3.9	4.4±5.3	3.9
Threonine	4.5±6.8	3.1	3.6±4.1	4.0
Tryptophan	Đ	0.3	3.0	1.3
Valine	4.0±5.2	4.9	5.1±6.9	6.4
Alanine	5.5±7.0	6.1	6.3±6.7	7.4
Arginine	4.3±8.7	14.9	4.6±5.1	16.4
Aspartic acid	6.0±11.8	6.5	8.5±18.5	7.0
Glutamic acid	11.7±23.4	6.9	6.7±9.9	7.2
Cysteine	Đ	Đ	Đ	Đ
Glycine	6.3±7.5	5.2	4.9±13.3	7.2
Proline	5.0±10.5	4.0	1.8±4.4	6.4
Serine	5.6±6.1	3.0	4.0±6.2	2.9
Tyrosine	4.4±4.7	1.4	1.3±3.4	2.4

Table 3: Mineral compositions of seaweeds compared to whole foods

Food Type	Calcium	Potassium	Magnesium	Sodium	Copper	Iron	Iodine	Zinc
Seaweed								
(mg/100 g wet weight)*								
Ascophyllum nodosum	575.0	765.0	225.0	1173.8	0.8	14.9	18.2	NA
Laminaria digitata	364.7	2013.2	403.5	624.6	0.3	45.6	70.0	1.6
Himanthalia elongata	30.0	1351.4	90.1	600.6	0.1	5.0	10.7	1.7
Undaria pinnatifida	112.3	62.4	78.7	448.7	0.2	3.9	3.9	0.3
Porphyra umbilicalis	34.2	302.2	108.3	119.7	0.1	5.2	1.3	0.7
Palmaria palmata	148.8	1169.6	97.6	255.2	0.4	12.8	10.2	0.3
Chondrus crispus	373.8	827.5	573.8	1572.5	0.1	6.6	6.1	NA
Ulva spp.	325.0	245.0	465.0	340.0	0.3	15.3	1.6	0.9
Enteromorpha spp.	104.0	351.1	455.1	52.0	0.1	22.2	97.9	1.2
Whole food								
(mg/100 g weight)†								
Brown rice	110.0	1160.0	520.0	28.0	1.3	12.9	NA	16.2
Whole milk	115.0	140.0	11.0	55.0	Tr	0.1	15.0	0.4
Cheddar cheese	720.0	77.0	25.0	670.0	0.0	0.3	39.0	2.3
Sirloin steak	9.0	260.0	16.0	49.0	0.1	1.6	6.0	3.1
Lentils green and brown	71.0	940.0	110.0	12.0	1.0	11.1	NA	3.9
Spinach	170.0	500.0	54.0	140.0	0.0	2.1	2.0	0.7
Bananas	6.0	400.0	34.0	1.0	0.1	0.3	8.0	0.2
Brazil nut	170.0	660.0	410.0	3.0	1.8	2.5	20.0	4.2
Peanuts	60.0	670.0	210.0	2.0	1.0	2.5	20.0	3.5

*Values for seaweeds from the Institut de Phytonutrition (2004).[34]
†Values for whole foods from McCance *et al.* (1993).[67]

Table 4: Anti-HPV and related anticancer agents from seaweeds

Marine Organisms	Specific Compounds	Mechanisms of Action
	λ-carrageenan[4,65]	Blocking HPV infection
Red Algae	κ-carrageenan[4,65]	Blocking HPV infection
	ι-carrageenan[4,65]	Blocking HPV infection
	Agar[4]	Blocking HPV infection
Brown Algae	Alginic acid[4,66]	Inhibiting HPV and cancer cell proliferation
	Fucoidan[4]	Blocking HPV infection

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