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Review Article

Potential of Seaweed *Ulva Fasciata* and its Derived Compounds Against Prostate Cancer - A Mini Review

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ABSTRACT

Cancer is a multifactorial group of diseases defined by the uncontrolled growth of cells. Prostate cancer is the second leading cancer in men and the fifth leading cause of death worldwide. However, the incidences of cancer have increased steadily over the years. Lifestyle changes and genetic factors are the leading causes of cancer. Seaweeds have been a source of food since ancient times, and studies have reported low incidences of cancers in countries consuming seaweed-rich diets. Marine macroalgae Ulva belonging to the family *Ulvaceae* have been reported to possess anticancer potential which is dominating the coastal regions of the world and across the coastal belt of India. Several studies have indicated that compounds extracted from seaweeds act as an effective anticancer agent. The biological benefit of seaweed potential in treating cancers was identified through epidemiological studies that showed a low incidence of the disease in both men and women consuming seaweed countries. By considering the potential of compounds present in the seaweeds to act against cancer cells, this review focuses on the multistep *in vitro* study protocol of deriving the crude seaweed extract and its identification. It also highlights the anticancer potential of seaweeds by MTT Assay and calls attention to the potential of compounds extracted from seaweed *Ulva fasciata* and *Ulva lactuca* and their effects against prostate cancer.

Keywords: Prostate Cancer; Ulva fasciata; Ulva lactuca; Epidemiology; Incidence; Extraction; Seaweed Compound

1 INTRODUCTION

Cancer is a life-threatening disease with tremendous negative implications. In the 21st century, it is endangering the health and life of humans [1]. In all cancer types, some cells of the body begin to divide without stopping, forming an uncontrolled growth of cells that spread into surrounding tissues and can concurrently start anywhere in the human body [2]. Cancer is the second leading cause of death in the world after cardiac disease. Cancer incidence increased steadily in both developed and developing countries from 12.7 million cases in 2008 to 14.1 million cases in 2012, with the number of people dying up from 7.6 million people in 2008 to 8.2 million people in 2012 [3]. Cancer deaths are expected to rise to 13.0 million by the end of 2030. Most deaths associated with cancer occur in low-and middle-income countries with limited access to medical resources and health systems. According to the 2022 report 1,918,030 new cancer cases and 609,360 cancer deaths have been estimated to occur [4].

Prostate cancer is one such cancerous tumour worldwide. Prostate cancer cells spread by breaking away from prostate tumour. They can travel through blood vessels or lymph nodes to reach other parts of the body. After dispersal, cancer cells attach to other tissues and grow to form new tumours, causing damage where they land [5]. Prostate cancer is an age-related disease with a steadily increasing incidence. The incidence rate of prostate cancer varies across regions and populations. It is the second most frequent malignancy in men worldwide [6]. Prostate cancer is the most common cancer in American men. According to the American Cancer Society's estimates about 288,300 new Prostate cancer cases have occurred and 34,700 men have died from cancer [7]. Over the years, there has been an increase in the associated search for new foods or supplements that can help prevent the occurrence of cancer. It was observed that mainly the western diet strategies and their respective lifestyle are favourable for the growing cancer incidence [8].

The possibilities to treat cancer are surgical, chemotherapy, radiotherapy, cancer-targeted therapy, and immunotherapy. Chemotherapy is the principal treatment method applied to treat cancer [9]. However, these therapies have massive side effects due to their high dosages on the patients. This has led to the enhanced search for new natural compounds that can be used as anti-cancer therapeutics drugs [10]. The cost-effective and non-invasive tools to reduce cancer incidence by destroying cancer cells. It has been achieved by aiming attention towards natural compounds derived from marine habitats, which contain an interesting source of compounds [11]. It has been shown that East Asia populations have shown reduced cancer incidence due to the consumption of seaweeds for a long time as compared to Western countries.

Seaweeds or marine macroalgae are primitive types of plants that lack leaves, true stems, and roots. Approximately more than 15,000 seaweeds were found to be present in the intertidal zones and tropical waters of the ocean [12]. There are about 6500 red seaweeds (Rhodophyta), 1500 species of green seaweed (Chlorophyta), and 1800 brown species (Phaeophyta) found in nature. Seaweeds are widely used as functional foods and medicinal herbs all over the globe, particularly with a long history in Asian countries [13]. It can be consumed directly or used as an ingredient in many dishes. They are used in traditional Chinese medicine to treat goiter, swelling, pain in the testes, and edema. Seaweed products are mainly utilized in the food industry, as a component of fertilizers, in animal feed supplements, and as additives for human food [14].

India is a major hub of seaweedsthat flourish abundantly along the Indian coastline, particularly in the rocky shore regions.Rich seaweed beds are identified to occur around Visakhapatnam's eastern coast; Mahabalipuram, Gulf of Mannar, and Kerala in the southern coast; Veraval and Gulf of Kutch in the Western coast; Andaman and Nicobar Islands and Lakshadweep. These macroalgae are also abundant around Mumbai, Ratnagiri, Goa, Karwar, Vizhinjam, and Pulicat in Tamil Nadu and Chilka in Orissa [15].

One such marine macroalgae dominating the coastal regions of India is Ulva or sea lettuce species belonging to the family Chlorophyceae [16]. It occurs plenteously in South Indian coastal areas. Seaweeds have recently received attention in the protection and treatment of cancer. *Ulva fasciata* and *Ulva lactuca* are among these traditional products [17]. *Ulva lactuca* is a widespread macroalga occurring at all levels of the intertidal zone, in calm and protected harbors as deep as 10m and northern climates [18]. It grows along rocky or sandy coasts of oceans and estuaries. *Ulva fasciata* occurs bountifully in the coastal regions. It is known for its medicinal and antioxidant properties which grow on intertidal rocks, in tidepools, and on reef flats [19]. Recent studies showed that these seaweeds are potent anticancer agents because of their anti-proliferative activity and antigenotoxic effect in human cancer cell lines and cancer-inhibiting activity in experimental models [20]. Various studies have discussed seaweed-derived natural products and their anticancer potential. This review focuses on the anti-cancer potential of seaweed *Ulva spp.* and its derived natural compounds against prostate cancer.

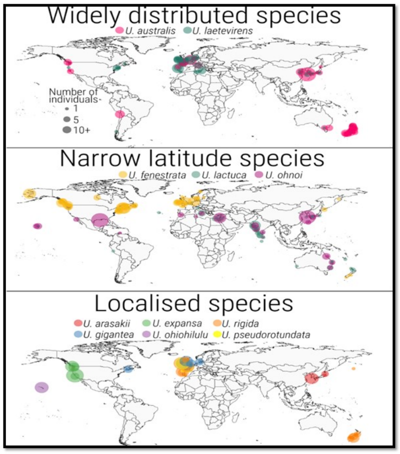
1.1 Collection and identification of seaweed

The genus Ulva is one of the most numerous marine algae flourishing abundantly on coastal regions growing on rocky shores. *Ulva spp.* withstands the extreme environmental conditions of the earth's ponds and salty seas [21]. Ulva species are difficult to morphologically identify due to their phenotypic plasticity. However, combined molecular and morphological techniques can lead to better characterization of the species. DNA barcoding is a taxonomic method that uses a short genetic marker in an organism's DNA to identify it. In recent years studies conducted on *Ulva spp.* Showed that these macroalgae are massively distributed over the coastal belts of the world [22]. The species were collected from the Persian Gulf on the coast of Bandar-Abbas, Hormozgan province, Iran, the intertidal region of Mandapam, Tamil Nadu, India, south coast areas like Rameswaram and Keelakarai, Tamil Nadu, India, Parangtritis beach, Yogyakarta, Central Java, Indonesia, intertidal rocky surface of Visakhapatnam coast, Andhra Pradesh, India, Egyptian shores [23]. Worldwide distribution of seaweeds (Figure 1). These seaweed samples are washed clean with seawater and thoroughly shade-dried with absorbent paper.

1.2 Extraction methods

The extract preparation method of seaweeds comprises seaweed on selection, impurity removal, weak acid washing, mincing, and homogenizing. The obtained liquid product is an active seaweed extracting solution, or it can be prepared into active seaweed extract powder through drying, and the extracting solution and the extract powder are collectively called active seaweed extract [24]. The coarsely powdered seaweeds are subjected to three types of solvents like ethanol, methanol, and hydro-alcohol for extract preparation. Several seaweeds when subjected to these solvents yield crude extracts that have the potential to destroy cancer cells [25].

Studies showed that the ethanolic extracts of *Ulva lactuca L.*, possesses rich antioxidant property and it also has anti-cancer potential to kill the blood cancer cells in the human body. *Ulva fasciata* methanolic extracts proved to be an outstanding antioxidant, anti-microbial and anti-cancer



(Antoine Fort et al., 2021) [Source: Ref. 26]

Figure 1: Worldwide distribution of Ulva species

candidate, the crude hydro-methanolic extracts of *Ulva fasciata* and *Ulva lactuca* shows cytotoxic effects due to the higher phenolic and flavonoid content [26].

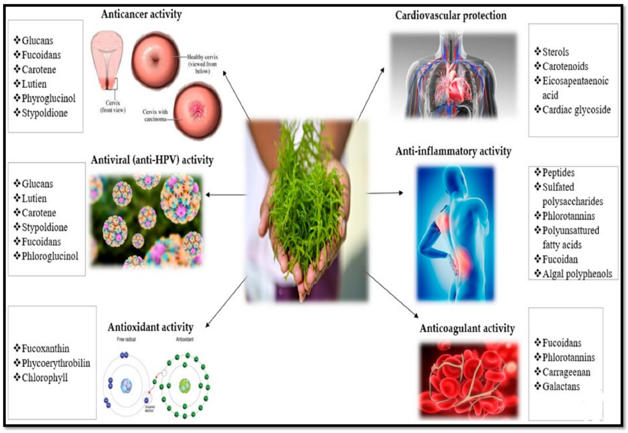
1.3 Seaweed and its secondary metabolites

Several epidemiological records around the world, have proposed that cancer is an avoidable disease. As mentioned before, in some countries, mainly in East Asia there is a high amount of seaweed consumption which is rich in biologically active metabolites and other macro and micronutrients that regulate the good function of the human body [27]. Seaweeds possess high nutritional potential (Table 1). Seaweed-derived compounds have been studied and show a wide range of bioactive potentials, such as anti-bacterial, anti-diabetic, anti-allergic, anti-cancer, (Figure 2), and antioxidant properties [28]. Several bioactive compounds such as fatty acids, sterols, carotenoids, polysaccharides, dietary fibers, alginate, agar, phyco-colloids, and carrageenan are found to be present in seaweeds. Apart from secondary metabolites, seaweeds are a rich source of sulphated polysaccharides that have been reported to have anti-tumor, antiangiogenetic, cytotoxic, and immunostimulating properties. Polysaccharides such as fucoidan, alginate, agarose, and carrageenan represent a very fascinating group of macromolecules that are widespread and have been in more attention in the biochemical and medical areas due to their anti-cancer effects [29].

The GC-MS analysis of seaweed *Ulva lactuca* linnshowed that the seaweed contains 17 phyto-compounds i.e. 7-Hexadecene, (Z) (1.50 %), 8-Heptadecene (3.78%), Tetradecanoic acid, ethyl ester (CAS) (2.07%), Phytol 2-Hexadecen-1-ol, 3,7,11,15-tetramethyl-, [R-[R*,R*-(E)E)]-(CAS)(10.51%), Doconexent (2.24), Hexadecanoic acid (CAS) (3.18%), Hexadecanoic acid, ethyl ester (20.24%), Ethyl 6,9,12,15-octadecatetraenoate (3.35%), (E)-9-Octadecenoic acid ethyl ester (9.59%), Octadecanoic acid, ethyl ester (1.66%), Hexadecanoic acid, 2,3-dihydroxypropyl

Table 1: Seaweeds with their anti-cancer potential

Seaweed	**Family**	**Active extracts**	**Biological activity**	
Ulva fasciata Delile	*Ulvaceae*	Methanol	• Antioxidant activity • Anti-cancer activity against HepG2 cell • Antimicrobial activity	[9]
Ulva lactuca *Ulva fasciata*	*Ulvaceae Ulvaceae*	Hydro-methanol	• Anticancer activity against breast cancer cell lines MCF-7 and MDA-MB-231	[10]
Ulva lactuca *Ulva fasciata* *Amphiroa anceps* *Corallina mediterranea*	*Ulvaceae Ulvaceae Lithophyllaceae Corallinaceae*	Methanol: hexane	• Anticancer activity against human breast adenocarcinoma cell line (MCF-7) and colorectal carcinoma cell line (HCT-116).	[5]
Ulva lactuca L.	*Ulvaceae*	Ethanol	• Antioxidant activity • Anti-cancer activity using blood cancer MOLT-3 cell line.	[11]
Chaetomorpha sp.	*Cladophoraceae*	Ethanol	• Antioxidant activity • Anti-cancer against breast cancer cell lines MCF-7 and MDA-MB-231	[14]
Ulva lactuca *Eucheuma cottonii*	*Ulvaceae* *Solieriaceae*	n-hexane Chloroform Ethyl acetate Ethanol	• Anticancer activity against breast cancer cell line MCF-7 and Colon HCT-116 cells.	[2]



(Marius Alexandru Moga et al., 2020) [32]

Figure 2: Health-promoting effects of seaweeds and their derived compounds

ester, (n)(1.77%), 2-(2-mercaptopro-2-nyl-aminoimino)-pentane (2.29%), Hexadecanoic acid, 1,1-dimethyl-1,2-ethanediyl ester (CAS) (1.17%), Heneicosane (CAS) (1.83%), Heptacosane (CAS) (2.02%), Nonacosane (CAS) (3.83%) and Dodecane, 5,8-diethyl (2.07%) [30]. These bioactive compounds from the seaweed possess several bio-activities like pulmonary edema, irritation, diarrhea, muscle weakness, anemia, respiratory failure, and drowsiness. *Ulva fasciata* and *Ulva lactuca* show higher cytotoxic effects due to their higher phenolic and flavonoid content. The ethyl acetate and water extracts show the highest total phenolic contents in Ulva rigida possessing promising antioxidant activity [31].

1.4 Anti-cancer potential of seaweeds and their derived compounds

Cancer is a multifactorial disease of multiple causes. It occurs mainly by acquired genetic changes, which results in tumour cells gaining survival or growth advantages. The occurrence of cancer is a complicated process with multiple factors and steps, which are related to infection, smoking, occupational exposure, environmental pollution, genetics, junk diet, and other factors. Biological factors such as cell differentiation and proliferation abnormality, loss of growth control, invasiveness, and metastasis [32].

Epidemiological studies have shown that all common cancers vary in incidence from to place and from time to time. Variations have not been easy to establish because of differences in the provision and utilization of medical resources and changes in terminology and methods of diagnosis [33]. Cancer of the bladder accounts for 7% of all cancers in men in the area with the highest recorded incidence and accounts for over 20% of all cancers in men in Southern Malawi and the Southwest corner of Kenya. It is difficult to be sure about the absence of a disease based on a small survey. Surveys in Africa and Asia have, not been practical in the least developed areas as these areas are likely to have the lowest incidence of cancers that are in western society [34]. Head basal cell carcinoma of the skin of the face, which affects more than half the fair-skinned population of Queensland by 75 years of age, the scar epitheliomas of the leg that develop on the site of old ulcers in Africa and account for between 10 and 20% of all cancers seen in some Malawi. Lung cancer was the most common cancer in 1990, with 1.04 million new cases, or 12.8% of the world's total [35]. Developed countries account for about 58% of the total lung cancer. It is by far the most common cancer of men (18% of the total) with the highest rates observed in North America, and Europe. Comparatively stomach cancer was the second most frequent cancer in 1990 and new cases estimated were 7,98,000 new cases [36]. Developing countries accounted for about 60% of the cases. The highest incidence rates were observed in Japan, East Asia, South America, and Eastern Europe. It was observed that the incidence in Central Africa was not particularly low [36]. The third most cancer observed in the world today is breast cancer, which is the most common tumour in women. It is the most common cancer of women in all the developed areas except for Japan as it is in Northern Africa, South America, East, Southeast, and Western Asia and Micronesia/Polynesia [37]. The age-standardized incidence is highest in North America (86.3 per 10^5) and lowest in China (11.8 per 10^5). Prostate cancer is the cause of mortality among men, and each year 1.6 million men are diagnosed with and 366,000 men die of prostate cancer. It is the second most frequent cancer diagnosis made in men and the fifth leading cause of death worldwide. Based on GLOBOCAN 2018 estimates 1,276,106 new cases of prostate cancer were reported worldwide in 2018, with higher prevalence in developed countries [38].

With the advancements in cancer detection and treatment and better survival rates, management and reduction of treatment-associated side effects are increasingly important in maintaining the quality of life. The high-dosage cancer treatments also follow severe side effects in patients [39]. The effective cancer therapies are not cell-specific, as they target normal healthy cells of the body along with the tumour cells (Figure 3). The high-dosage chemotherapies destroy the normal cells and cause various side effects like fatigue, hair loss, and anemia. However, advancements in naturally derived compound-targeted cancer cell treatments are in the various clinical trials for their potential of lower to no side effects [40]. The products derived from the sea or the marine environment serve as a promising source of developing drugs for the treatment of deadly diseases like cancer.

The use of marine organisms in traditional medicine does not have a long history. Marine natural products have been playing a vital role in the area of drug discovery since the 1950s. Several marine natural products are in various phases of clinical development, mainly in the area of cancer research [41]. Marine-derived anticancer agents exhibit their

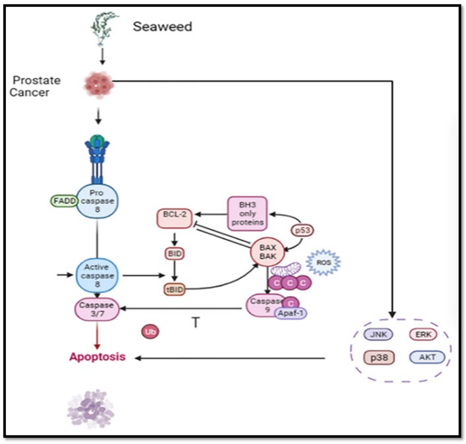


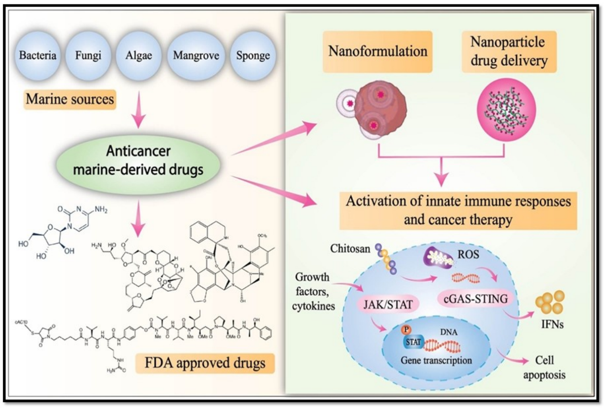
Figure 3: Possible mechanism of cancer cell death due to seaweed

activity through several mechanisms of action on a wide range of biological targets (Figure 4). Mitosis, apoptosis, cell cycle, DNA synthesis, signal transduction, angiogenesis, multidrug efflux, and mitochondrial respiration are the most common anti-cancer drugs (Table 2). Approximately 150 compounds were found to be cytotoxic against various tumour cells [42]. The benefits of eating seaweed were identified through epidemiological studies that showed the low prevalence of diseases such as coronary heart disease and diet-related cancer in countries with high-seaweed consumption. It has been postulated that dietary seaweed consumption confers protection against cancer [43]. Cancer incidence is much lower among the population who consume a seaweed-rich diet, such as in Asia, in comparison with those who consume a Western-style diet. Various compounds extracted from a range of seaweeds have been shown to eradicate or slow the progression of cancers [44].

The species of green macroalga belonging to the genus Ulva possess cytotoxic potential. Cytotoxicity testing is carried out *in vitro* with cells or *in vivo* using experimental animal models [45]. Recent studies developed anti-cancer effects of *Ulva lactuca*, *Ulva australis, Ulva rigida,* and *Ulva ohnoi* using human cancer cell lines [46]. The cell lines include LNCap (Low metastatic prostate cancer cell line), DU-145 (Moderately metastatic prostate cancer cell line) and PC-3 (Highly metastatic prostate cancer cell line), HepG2 (hepatocellular carcinoma), MCF7 (human breast cancer), and HeLa (cervical cancer). The most widely used principal method of cytotoxicity testing is MTT Assay. MTT assay helps to determine the dosage-dependent cancer cell death.

Table 2: Marineseaweedsand their derivedsecondary metabolites

Seaweed	Active Extract	Secondary Metabolite	Activity	
Ulva lactuca	1.n-hexane 2.Chloroform 3. Ethyl-acetate 4. Ethanol	• Sterols, • Flavonoids, • Triterpenoids, • Glycosides, • Phenol, • Coumarin, • Saponin, • Tannin	• Anticancer activity against breast cancer cell line MCF-7 and Colon HCT-116 cells.	[2]
Amphiroa anceps *Ulva fasciata*	1.Methanol: hexane	• Terpenes • Steroids	• Anticancer activity against human breast adenocarcinoma cell line (MCF-7) and colorectal carcinoma cell line (HCT-116).	[5]
Chaetomorpha	1. Ethanol 2. Water	• Flavonoid • Phenol, • Tannin	• Antioxidant activity • Anticancer activity against human cancer cell lines MCF-7 and MDA-MB-231	[14]
Ulva lactuca	1.Methanol 2. Ethyl acetate 3.Chloroform 4.Petroleum ether 5. Acetone 6. Hexane	• Carbohydrate, • Saponin, • Flavonoids, • Steroids, • Tannin • Alkaloids, • Terpenoids, • Protein, • Phenol	• Anticancer • Anti-inflammatory • Antimicrobial • Antioxidant	[32]



(Saeed AF et al., 2021) [35]

Figure 4: Marine-derived drugs – recent advances in cancer therapy

2 CONCLUSION

Natural products for food and medicinal aspect are used for several decades. The marine environment is one of the richest sources of various secondary metabolites. Over the past few decades, various anti-cancer studies have been performed to determine the potential of natural extracts or natural products obtained from seaweeds to kill cancer cells. The crude extracts of Ulva have shown cytotoxicity against various human cancer lines and proved to be an appropriate anti-cancer drug candidate. Seaweed consumption and its association with cancer have been proved by the epidemiological reports of cancer incidences in East Asia countries and Western countries. The treatment strategies for cancer with severe side effects must progress in developing drugs from natural resources. However, further research is needed to understand the beneficial value of seaweed-derived compounds and their application in treating various diseases and improving the quality of life.

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