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MARINE ALGAE: AN EXTENSIVE REVIEW OF MEDICINAL & THERAPEUTIC INTERESTS

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ABSTRACT

The global economic impact of the five leading chronic diseases — cancer, diabetes, mental illness, CVD, and respiratory disease — could reach $47 trillion over the next 20 years, according to a study by the World Economic Forum (WEF). According to the WHO, 80% of the world's population primarily those of developing countries rely on plant-derived medicines for healthcare. The purported efficacies of seaweed derived phytochemicals areshowing great potential in obesity, T2DM, metabolic syndrome, CVD, IBD, sexual dysfunction and some cancers. Therefore, WHO, UN-FAO, UNICEF and governments have shown a growing interest in these unconventional foods with health-promoting effects. Edible marine macro-algae (seaweed) are of interest because of their value in nutrition and medicine. Seaweeds contain several bioactive substances like polysaccharides, proteins, lipids, polyphenols, and pigments, all of which may have beneficial health properties. People consume seaweed as food in various forms: raw as salad and vegetable, pickle with sauce or with vinegar, relish or sweetened jellies and also cooked for vegetable soup. By cultivating seaweed, coastal people are getting an alternative livelihood as well as advancing their lives. In 2005, world seaweed production totaled 14.7 million tons whichhas more than doubled (30.4 million tons) in 2015. The present market value is nearly $6.5 billion and is projected to reach some $9 billion in the seaweed global market by 2024. Aquaculture is recognized as the most sustainable means of seaweed production and accounts for approximately 27.3 million tons (more than 90%) of global seaweed production per annum. Asian countries produced 80% for world markets where China alone produces half of the total demand. The top six seaweed producing countries are China, Indonesia, Philippines, Korea, and Japan.

Keywords: seaweeds; cancer prevention; hyperglycemia management; microalgae; neuroprotection; alimentary disorders.

Figure 1: Seaweed Farming. According to FAO of the UN, nearly 45% of the female workforce is working in agriculture. Seaweed farming is surely a step toward gender equality (Source: SOFA Team and Cheryl Doss, the role of women in agriculture, ESA Working Paper No. 11-02, March 2011).

OBESITY, HYPERTENSION AND HYPERGLYCEMIA MANAGEMENT

According to the WHO, 2.3 billion adults are overweight and the prevalence is higher in females of childbearing age than males [1].In the US, the economic burden of obesity is estimated to be about $100 billion annually [2]. Worldwide obesity causes 2.8 million deaths per year and 35.8 million disability-adjusted life-years, some 45% of diabetes, 25% of IHDs and up to 41% of certain cancers [3]. Four major bioactive compounds from seaweeds which have the potential as anti-obesity agents are fucoxanthin, alginates, fucoidans and phlorotannins [4]. Alginates are amongst the seaweed fibers that are well-known for their anti-obesity effects. They have been shown to inhibit pepsin, pancreatic lipase [5], reduced body weight, BMI, and the blood glucose level [6], ameliorate fat accumulation, TG and TC [7] in experimental animals. Koo et.al, 2019 reported Fucoxanthin powder developed from microalga *Phaeodactylum tricornutum* (Bacillariophyta) plus CLA or Xanthigen improved lipid metabolism, reduced body weight gain and adipose tissue [8]. Individually, fucoxanthin lowers glycated hemoglobin, especially in healthy subjectswith a certain UCP1 genotype [9]. Mendez et. al, 2019, reported anti-obesogenic potential of seaweed dulse (*Palmaria palmata*) (Rhodophyta) (**Figure 2**) in high-fat fed mice [10]. Seca et.al, 2018 suggested that small peptides from seaweed may possess bioactivity, for example, of relevance for BP regulation [11]. Yang et.al, 2019 reported Fucoidan A2 from the brown seaweed *Ascophyllum nodosum* (Ochrophyta, Phaeophyceae) (**Figure 3**) lowers lipid by improving reverse cholesterol transport in mice [12]. Sørensen et.al, 2019 reported improved HbA1C and lipid profile with *Saccharinalatissima* (Ochrophyta, Phaeophyceae) or sugar kelp (**Figure 4**) in mice [13]. Fucoidan taken twice daily for a period of 90 days did not markedly affect insulin resistance in obese, nondiabetic cohort [14], but attenuates obesity-induced severe oxidative damage [15], show anticoagulant activity [16], suppress fat accumulation [17], may improve obesity-induced OA [18], antioxidant and lipolytic activities [19]. Catarino et.al, 2017 and 2017 reported *Fucus vesiculosus* (Ochrophyta, Phaeophyceae) (**Figure 5**) phlorotannin-rich extracts have significant effect on α-glucosidase, α-amylase and pancreatic lipase [20]. Phlorotannins, farnesylacetones and other constituents from seaweeds—have also been described for their potential use in hypertension due to their reported vasodilator effects [21]. Sun et.al, 2019 reported the hydrogen bond and Zn (II) interactions between the peptides of Marine Macroalga *Ulva intestinalis*(Chlorophyta) and ACE [22]. In similar studies, peptides from *Sargassum siliquosum*, *Sargassum polycystum* [23], *Fucus spiralis*(Ochrophyta, Phaeophyceae) [24], *Palmaria palmata* [25], *Pyropia yezoensis*(Rhodophyta),*Undaria pinnatifida*(Ochrophyta, Phaeophyceae),*Ulva clathrate* (formerly *Enteromorpha clathratclathrate*),*Ulva rigida*(Chlorophyta), *Gracilariopsis lemaneiformis*, *Pyropia columbina*(Rhodophyta), *Ecklonia cava*, *Ecklonia stolonifera*, *Pelvetia canaliculata*, *Sargassum thunbergii*(Ochrophyta,Phaeophyceae)[26], *Pyropia yezoensis* (formerly *Porphyra yezoensis*) *[27]*, *Fushitsunagiacatenata* (formerly *Lomentaria catenata*), *Lithophyllum okamurae*, *Ahnfeltiopsisflabelliformis* (Rhodophyta)[28] show potential ACE inhibitory activities.Besides the activation of Ag II, ACE plays a concomitant role in the regulation of hypertension via the inactivation of an endothelium-dependent vasodilatory peptide, bradykinin [28,29]. Kammoun et.al, 2018 reported hypolipidemic and cardioprotective effects of *Ulva lactuca* (Chlorophyta), which effectively counteracts cardiotoxic effects of hypercholesterolemic regime [30]. In several studies Ulva species showed hypotensive, hypoglycemic, hypolipaemic and antiatherogenic properties [31-40]. Moreover, studies also support seaweed-induced effects of postprandial lipoproteinemia [41-43],postprandialhyperglycemia [44-55], lipid metabolism and atherosclerosis [56-70], reduced body weight [71-80], HbA1c [13], [34], [52], [55], [81-90], reduced BP/episodes of hypertension [11], [26], [28], [46], [49], [53], [66], [80], [91-102] and prevented obesity-induced oxidative damage [4], [8], [13], [34], [103-120].Increased seaweed consumption may be linked to the lower incidence of metabolic syndrome in eastern Asia[28].

Figure 2: ***Palmaria palmata***(Source: What is Dulse Seaweed? Mara Seaweed October 17, 2017).

Figure 3: ***Ascophyllum nodosum*** (Source: Ascophyllum nodosum. Jiloca Industrial, S.A. Agronutrientes Blog)

Figure 4: *Saccharina latissima* or sugar kelp (Source: Nature Picture Library).

Figure 5:. *Fucus vesiculosus* L. (Source: Seaweed Site of M.D. Guiry)

Cancer Prevention & Tumor Control

In 2019, 1,762,450 new cancer cases and 606,880 cancer deaths are projected to occur in the United States [121]. Globally, cancer is responsible for at least 20% of all mortality [122], 18.1 million new cancer, 9.5 million deathin 2018 [123,124], the 5- year prevalence of 43.8 million [125], is predicted to rise by 61.4% to 27.5 million in 2040 [126]. Approximately 70% of deaths from cancer occur in LMICs [127]. Asia, Africa, and Latin America are collectively home to more than 50% of cancer patients; with more than half of global cancer-related mortalities occurring in Asia alone [128]. Cancer causes 46 billion in lost productivity in major emerging economies [129] and economic costs of tobacco-related cancers exceed USD 200 billion each year [130]. Compounds from natural sources with anti-proliferative activity represent an important and novel alternative to treat several types of cancer. *Egregia menziesii*(brown seaweed) (**Figure 6**) [131], *Portieria hornemannii* [132], *Grateloupia elliptica*(Rhodophyta)[133],*Sargassum serratifolium*[134], Chitosan alginate (polysaccharide from seaweeds) [135-143], xanthophylls(astaxanthin, fucoxanthin) and Phlorotannins (phloroglucinol) obtained from the microalgae [144-155], are reported in brain tumor (glioblastoma) studies.Astaxanthin and fucoxanthin are major marine carotenoids. Major seaweed algae sources of astaxanthin mono- and di- esters are the greenmicroalgae (Haematococcus lacustris - formerly Haematococcus pluvialis (Figure 7), *Chromochloris zofingiensis* - formerly *Chlorella zofingiensis*, Chlorococcum)and red-pigmented fermenting yeast*Phaffia rhodozyma* [156,157].Fucoxanthin is present in Chromophyta (*Heterokontophyta* or *Ochrophyta*), including brown seaweeds (*Phaeophyceae*) and diatoms (*Bacillariophyta*) [158]. Several 2019 reviews discuss use of fucoidans (sulfated polysaccharide mainly derived from brown seaweed) in lung cancer management. Brown algae like *Fucus vesiculosus*, *Turbinaria conoides*, *Saccharina japonica* (formerly *Laminaria japonica*) (**Figure 8**) are reported in inhibition of tumor migration and invasion, apoptosis induction, and inhibition of lung cancer cell progression respectively [159]. *Fucus distichus* subsp. *evanescens* (formerly *Fucus evanescens*), *Sargassum* sp. (**Figure 9**), and *Saccharina japonica*were reported to inhibit proliferation and metastasis and induce apoptosis *in vitro* [160]. *Undaria pinnatifida* acted on ERK1/2 MAPK and p38, PI3K/Akt signaling;*F. distichus* subsp. *evanescens* (formerly *F. evanescens*)increased metastatic activity of cyclophosphamide and showed cytolytic activity of natural killer cells in 2 different studies, and *F. vesiculosus* decreased NF-κB in LLC [161].*U. pinnatifida* was found to show average antitumor and superior efficacy against LLC in the review of Misra et.al, 2019 [162]. Sponge alkaloids from Aaptos showed potential in human lung adenocarcinoma A549, *Fascaplysinopsis* (Porifera)exerted an anti-proliferative and pro-apoptotic effect in lung cancer, and blue sponge Xestospongia showed apoptosis as well as stimulate anoikis in H460 lung cancer cells in review by Ercolano et.al, 2019[163].The most common breast cancer type is the invasive ductal carcinoma accounting for 70-80% of all breast cancers diagnosed [164]. Brown seaweed fucoidan inhibited human breast cancer progression by upregulating microRNA (miR)-29c and downregulating miR-17-5p, thereby suppressing their target genes [165]. *Lophocladia sp. (Lophocladines), Fucus* sp. *(fucoidan), Sargassummuticum* (polyphenol), *Pyropia dentata* (formerly *Porphyra dentata)* (sterol fraction),*Cymopolia barbata* (CYP1 inhibitors), *Agarophyton tenuistipitatum* (formerly *Gracilariatenuistipitata*) *Gracilaria termistipitata* was found to be effective in breast cancer studies[166].High Urokinase-type plasminogen activator receptor (uPAR) expression predicts formore aggressive disease in several cancer types [167], dietary seaweed may help loweringbreast cancer incidence by diminishing levels of uPAR [168]. The tropical edible red seaweed*Kappaphycus alvarezii* (formerly *Eucheuma cottonii)* (Figure 10) is rich in polyphenolsthat exhibited strong anticancer effect with enzyme modulating properties [169]. Jazzara et.al, 2016 concluded that λ-carrageenan (sulfated galactans found in certain red seaweeds) could be a promising bioactive polymer [170], as it showed a remarkable inhibitory effect on MDA-MB-231(triple negative breast cancer cell line) cell migration [171]. Several studies support polyphenols [172-176], flavonoids [177-186], fucoidan [159,160],[166], [187-195], lutein/zeaxanthin [196-200], otherseaweed alkaloids, peptides, tannins and polysaccharides [132], [164], [201-210] in breast cancer management. The number of deaths from colorectal cancer in Japan continues to increase [211], it is the third most common diagnosis and second deadliest malignancy for both sexes combined [212]. It has been projected that there will be 140,250 new cases of colorectal cancer in 2018, with an estimated 50,630 people dying of this disease [213]. High intake of red and processed meat and alcohol has been shown to increase the risk of colorectal cancer [214]. *U. pinnatifida* [159], [188], [215-221], *Saccharina latissima* [222], *Fucus vesiculosus* [117], [160], [223,224], *Sargassum hemiphyllum* (Ochrophyta, Phaeophyceae) [155], [225,226] have proven efficacy in this situation. Also, Algae derived astaxanthin [150], [227-232], fucoxanthin [233-237], lutein and zeaxanthin [238-241], polyphenols [242-246] have shown individual excellence.

Figure 6: *Egregia menziesii* brown seaweed (Source: University of British Columbia Garden).

Figure 7: *Haematococcus pluvialis* (Source: VERYMWL, Thailand)

Figure 8: *Saccharina japonica* (formerly *Laminaria japonica*) (Source: TCM Herbs)

Figure 9: *Sargassum* sp. (Source: POND5)

Figure 10: *Kappaphycus alvarezii* (formely*Eucheuma cottonii*) (Source: Blog at WordPress.com).

Neuroprotection in Stroke, Alzheimer's and Parkinsonism

Stroke is a leading cause for disability and morbidity associated with increased economic burden due to the need for treatment and post-stroke care. Acute ischemic stroke has enormous societal and financial costs due to rehabilitation, long-term care, and lost productivity. Between 2010 and 2030, stroke is expected to increase by more or less 60% in men and 40% in women [248]. Several studies reported neuroprotective role of astaxanthin and fucoxanthin [145], [248-268] in stroke prevention, Alzheimer's, Parkinsonism and other neurodegenerative diseases. Barbalace et.al, 2019 reported that marine algae inhibit pro-inflammatory enzymes such as COX-2 and iNOS, modulate MAPK pathways, and activate NK-kB [269]. *Neorhodomelaaculeata, Rhodomela confervoides* (Rhodophyta)[26], [270], *Ecklonia cava* (**Figure 11**)[271-275],*Saccharina japonica* (formerly *Laminaria japonica)* [276-281],*Fucus vesiculosus*[282-287], *Sargassum*spp. [288-295], *Saccorhiza polyschides* (Ochrophyta, Phaeophyceae) [283], *Codium tomentosum* [296], Ulva spp.(Chlorophyta), [256], [267], [293], [297-300], *Ecklonia maxima*(Ochrophyta, Phaeophyceae)[256], [301-303], *Gracilaria*spp. (**Figure 12**) [296], [304-311], *Gelidium pristoides*(Rhodophyta), [312,313], *Halimeda incrassata*(Chlorophyta)[314,315], *Alsidium triquetrum* (formerly*Bryothamniom triquetrum*) [316-318], *Chondrus crispus* (**Figure 13**) [319,320], *Hypnea valentiae*(Rhodophyta)(**Figure 14**) [298], *Ecklonia stolonifera*(Ochrophyta,Phaeophyceae) [321-323] were reported in several studies as neuro-protectives and suggested for use in neurodegenerative situations or are already in use in such conditions.

Figure 11: *Ecklonia cava* (Source: Predator Nutrition)

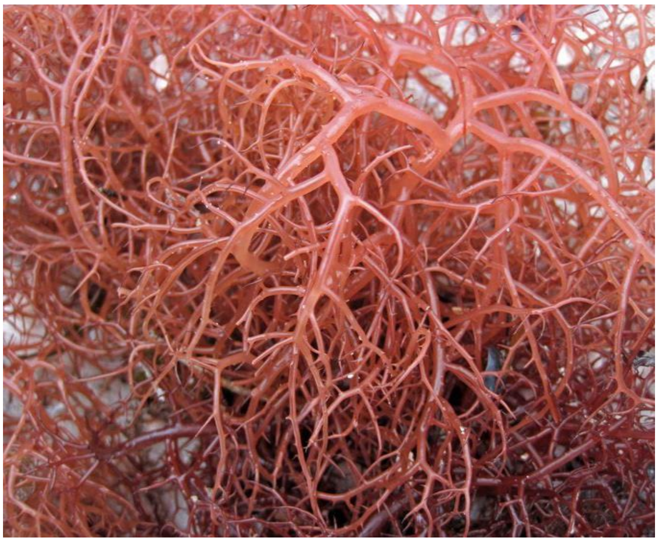

Figure 12: *Gracilaria tikvahiae*Red Seaweed (Source: Flickr)

Figure 13: *Chondrus crispus* - Carragheen or Irish Moss (Source: APHOTOMARINE)

Figure 14: *Hypnea valentiae* (Source: iNaturalist)

Alimentary Disorders

In the USA, the sales of prescription GI therapeutic drugs were $25 billion, the 10th leading therapeutic class in terms of sales [324], with $135.9 billion spent for GI diseases in 2015 [325]. Urbanization, western diet, hygiene, and childhood immunological factors are associated with IBD in Asia [326]. On the other hand, 14% of the global population is affected by IBS and 30% by constipation [327,328]. Na-alginate, has been used in the treatment of heartburn and GERD, although ESPGHAN/NASPGHAN Guidelines do not recommend it's use in chronic GERD [329,330]. The [^{13}C]-*Arthrospira platensis* (formerly *Spirulina platensis*)(Cyanobacteria) GEBT is an easy to measure of gastric emptying with accuracy [331-333].*Saccharina japonica* (formerly *Laminaria japonica*) (Ochrophyta, Phaeophyceae) (vomiting,hemorrhoids, IBD, probiotic synergist) [334,335], *Kappaphycus alvarezii* (formerly*Eucheuma cottonii*) (Rhodophyta) (IBD, hepatoprotective, anti-food allergy) [336-338],*Caulerpa mexicana* (Chlorophyta) (**Figure 15**) (Gastroprotective, IBD) [339-341], *Hypnea musciformis* (IBD) (Rhodophyta) [336], [342], *Fucus vesicolosus* (gastroprotective,ulcerative colitis) [117], [343], *Laminaria hyperborean*, *Laminaria digitatae* (IBD)[344,345], *Undaria pinnatifida* (Ochrophyta, Phaeophyceae) (**Figure 16**) (improves gut health)are reported for use in gut health modulation [346]. In addition, seaweed polysaccharides are atypical in structure to terrestrial glycans, and were found to resist gastric acidity, host digestive enzymes, and GI absorption [347]. Maternal seaweed extract supplementation can reduce both the sow fecal *Enterobacteriaceae* populations at parturition and piglet*E. coli* populations at weaning [348]. Also, seaweeds are good source of prebiotics that improve intestinal microbiota and may exert positive effects on IBD and IBS [349,350].

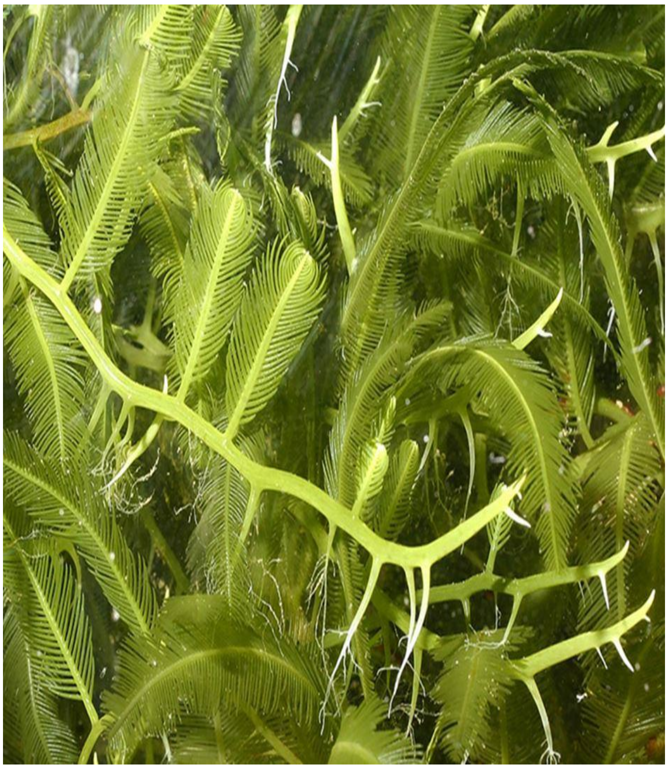

Figure 15: ***Caulerpa mexicana*** (Source: Reefs.com)

Figure 16: ***Undaria pinnatifida*** (Source: The Marine Life Information Network)

Thyroid Function

Seaweeds are a rich source of iodine and tyrosine [351], palatable and acceptable to consumers as a whole food or as a food ingredient, and effective as a source of iodine in an iodine-insufficient population [352]. In addition, daily diet should include thyroid boosting foods like those rich in iodine, the amino acid tyrosine, minerals like selenium, zinc, copper, iron, and various vitamins including, B2, B3, B6, C and E [353]. Edible seaweeds are rich in these vitamins and minerals [95]. Although, high iodine intake is well tolerated by most healthy individuals, ~~but~~ in some people, it may precipitate hyperthyroidism, hypothyroidism, goiter, and/or thyroid autoimmunity [354]. Excess intake of iodine through seafood consumption is a suspected risk factor for thyroid cancer [355]. Also, some sea weeds are contaminated with arsenic, mercury, cadmium and other heavy metals that have a positive association with thyroid hormones in adults [356-360].

Analgesic and Anti-inflammatory Potential

Neuropathic pain estimates are 60% among those with chronic pain. Mild -to-moderate pain may be relieved by non-drug techniques alone [128]. 1g of brown seaweed extract (85% *F. vesiculosus* fucoidan) daily could reduce joint pain and stiffness by more than 50% [361,362]. Association between algae consumption and a lower incidence of chronic degenerative diseases is also reported for the Japanese [363]. Carrageenan has been widely used as a tool in the screening of novel anti-inflammatory drugs [364]. Among others, *Pyropia vietnamensis* (formerly *Porphyra vietnamensis*) [365,366], *Kappahycus alvarezii* (formerly *Eucheuma cottonii*) [367], *Dichotomaria obtusata* (Rhodophyta) (**Figure 17**) [368], *Cystoseira sedoides, Cladostephus spongiosumis, Padina pavonica* (**Figure 18**) [369], *Ecklonia cava* (due to phlorotannins)(Ochrophyta, Phaeophyceae) [370-372],*Caulerpa racemosae* (Chlorophyta) [373], *Sarcodia ceylanica* [374], *Aactinotrichia fragilis*(Rhodophyta) [375], *Dictyota menstrualis* (Ochrophyta, Phaeophyceae) (**Figure 19**) [376],*Gracilaria cornea* [377], *Gracilaria birdiae* [378], class Phaeophyceae, Rhodophyta andChlorophyta [379], *Caulerpa curpressoides*[380,381], *Ulva lactuca* (Chlorophyta)(**Figure 20**) [382], *Sargassum swartzii* (formerly*Sargassum wightii) and Halophila ovalis* (Tracheophyta) [383], *Grateloupia lanceolatae(Rhodophyta)* [384], *Sargassum fulvellum and Sargassum thunbergii* [385], *Briareumexcavatum* (Octocoral) [386], *Caulerpa racemosae* (Chlorophyta) [387], *Sargassumhemiphyllum* (Ochrophyta, Phaeophyceae) [388], *Laurencia obtusa (Rhodophyta)* [389],*Caulerpa kempfii* [390], *Caulerpa cupressoides* (Chlorophyta) [391]are reported for their analgesic and anti-inflammatory properties.

Figure 17: *Dichotomaria obtusata*, Tubular Thicket Algae (reefguide.org)

Figure 18: Padina pavonica (Source: Alchetron)

Figure 19: *Dictyota menstrualis* (Source: flowergarden.noaa.gov)

Figure 20: *Ulva lactuca*, Sea Lettuce (Source: Addictive Reef Keeping)

Antimicrobial Properties

Rising antimicrobial resistance is a threat to modern medicine. Infections with resistant organisms have higher morbidity and mortality, are costlier to treat andestimated to cause 10 million deaths annually by 2050with global economic loss $100 trillion [392-394]. Lu et.al, 2019 reported *Saccharina japonica (formerly Laminaria japonica), Sargassum*(Ochrophyta, Phaeophyceae), *Gracilaria sp. and Pyropia* dentata (formerly *Porphyradentata)* (Rhodophyta) potentiated the activities of macrolides against *E. coli* [394].Carragelose® (first marketed product from algae) has the ability to block viral attachment to the host cells and being effective against a broad spectrum of respiratory viruses [395]. Besednova et.al, 2019 reported that fucoidans, carrageenans, ulvans, lectins, and polyphenols are biologically active compounds from seaweeds that target proteins or genes of the influenza virus and host components [396].

Table 1: Antimicrobial activity of different solvent extracts from seaweeds [397].

Red Seaweed	Organisms
Alsidium corallinum	*Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus*
Ceramium rubrum	*E. coli, Enterococcus faecalis, S. aureus*
Ceramium virgatum	*Salmonella enteritidis, E.coli, Listeria monocytogenes, Bacillus cereus*
Chondrocanthus acicularis	*E. coli, K. pneumoniae, E. faecalis, S. aureus*
Chondracanthus canaliculatus	*S. aureus, Streptococcus pyogenes*
Chondrus crispus	*L. monocytogenes, Salmonella abony, E. faecalis, P. aeruginosa*
C. crispus	*Pseudoalteromonas elyakovii, Vibrio aestuarianus, Polaribacter irgensii, Halomonas marina, Shewanella putrefaciens*
Ellisolandia elongata (formerly *Corallina elongataelongata)*	*B. subtilis, S. aureus, E. coli, Salmonella typhi, K. pneumoniae, Candida albicans*
Gelidium attenatum	*E. coli, K. pneumoniae, E. faecalis, S. aureus*
Gelidium micropterum	*V. parahaemolyticus, V. alcaligenes*
Gelidium pulchellum	*E. coli, E. faecalis, S. aureus*
Gelidium robustum	*S. aureus, S. pyogenes*
Gelidium spinulosum	*E. coli, E. faecalis, S. aureus*
Gracilaria dura	*V. ordalii, V. alginolyticus*
Gracilaria gracilis	*V. salmonicida*
Grateloupia livida	*S. aureus, E. coli, P. aeruginosa*
Gracilaria ornata	*E. coli*
Gracilaria subsecundata	*S. aureus, S. pyogenes*
Green Seaweed	
Boodlea composita	*V. harveyi, V. alginolyticus, V. vulnificus, V. parahaemolyticus, V. alcaligenes*
Bryopsis pennata	*V. vulnificus, V. parahaemolyticus*
Caulerpa lentillifera	*E. coli, Staphylococcus aureus, Streptococcus sp., Salmonella sp.*
Caulerpa parvula	*V. vulnificus, V. alcaligenes*
Caulerpa racemosa	*E. coli, S. aureus, Streptococcus sp., Salmonella sp.*
Chaetomorpha aerea	*Bacilus subtilis, Micrococcus luteus, S. aureus*
Chaetomorpha linum	*V. ordalii, V. vulnificus*
Cladophora albida	*V. harveyi, V. alginolyticus, V. vulnificus, V. parahaemolyticus, V. alcaligenes*
Cladophora glomerata	*V. fischeri, V. vulnificus, V. anguillarum, V. parahaemolyticus*
Brown Seaweed	
Chnoospora implexa	*S. aureus, S. pyogenes*
Cladophora rupestris	*E. coli, S. aureus, P. aeruginosa, V. harveyii, V. parahaemolyticus, V. alginolyticus*
C. rupestris	*E. coli, S. aureus, P. aeruginosa, V. harveyii, V. parahaemolyticus, V. alginolyticus*
C. rupestris	*E. coli, S. aureus, P. aeruginosa, V. harveyii, V. parahaemolyticus*
Colpomenia sinuosa	*S. aureus, S. pyogenes, B. subtilis, S. aureus, E. coli, S. typhi, K. pneumoniae, C. albicans*
Colpomenia tuberculata	*S. aureus, Sreptococcus pyogenes*
Cystoseira osmundacea	*S. pyogenes*
Cystoseira trinodis	*S. aureus, B. subtilis, E. coli, P. aeruginosa*
Dictyopteris delicatula	*S. aureus, S. pyogenes*
Dictyopteris undulata	*S. aureus, S. pyogenes*
Dictyota dichotoma	*S. aureus, B. subtilis, E. coli, P. aeruginosa*
Dictyota flabellata	*S. aureus, S. pyogenes*
Dictyota indica	*S. aureus, B. subtilis, E. coli, P. aeruginosa*
Dictyota sp.	*S. aureus, Enterococcus faecalis, P. aeruginosa*
Ecklonia bicyclis (formerly *Eisenia bicyclis*)	*S. aureus, S. epidermidis, Propionibacterium acnes*

Other Health Issues

Walsh et.al, 2019 reported osteogenic potential of brown seaweeds *Laminaria digitata* and*Ascophyllum nodosum* [398]. Seaweed contains several compounds with antioxidantproperties (phlorotannins, pigments, tocopherols, flavonoids, polyphenols andpolysaccharides) [399]. Antioxidant properties of *Fucus vesiculosus* and *Ascophyllum nodosum* (due to phlorotannins) [399], *Turbinaria conoides* (2H-pyranoids) [400], *Ulva clathratae* (Chlorophyta) (phenolics and flavonoid contents) [401], *Bifurcaria bifurcate* (**Figure 21**) (diterpenes eleganolone and eleganonal) [402], *Cystoseira* spp. (phenolicconstituents) [119], *Sargassum siliquastrum* (Ochrophyta, Phaeophyceae) (phenoliccompounds, ascorbic acid) [403], *Ulva compressa* (Chlorophyta) (phenolic contents) [404],*Saccharina japonica* (polysaccharides) and *Sargassum horneri* (Ochrophyta, Phaeophyceae)
(phenolic contents) [405,406], Halophila ovalis (**Figure 22**) and Halophila beccarii(Tracheophyta) (flavonoids) [407,408], *Cystoseira sedoides* (Ochrophyta, Phaeophyceae)(mannuronic acid than guluronic acid) [369], [409,410], *Caulerpa peltatapeltate*(Chlorophyta), *Gelidiella acerosa* (Rhodophyta), *Padina gymnospora*, and *Sargassum wightii*(phenols and flavonoids) [411], *Ecklonia cava* Kjellman (polyphenols) [412,413], *Undaria pinnatifida* (Ochrophyta, Phaeophyceae) (phlorotannins) [414] are well reported. Most othermedicinal effects are mainly due to presence of these antioxidants. Mesripour *et al.,* 2019reported antidepressant effects of *Sargassum plagyophylum* [415]. *Ecklonia bicyclis*, *Tribulus terrestris* (Magnoliophyta) improved sexual and ejaculation function and sexual QoL [416].Chronic pain is often associated with sexual dysfunction, suggesting that pain can reducelibido [416]. However, red algae (especially sea moss/ *Gracilaria* spp.), *Hypnea musciformis* (Vermifuge), *Monostroma nitidum* (formerly *Porphyra crispata*) are known to haveaphrodisiac properties [417-419]. Thrombotic diseases are reported to contribute to 30% earlydeaths globally [420]. *Ulva rigida* [421], *Udotea flabellum* (Chlorophyta) (**Figure 23**) [422],ulvans, and their oligosaccharides [380], *Nemacystus decipienus*, *Undaria pinnatifida*(Ochrophyta, Phaeophyceae) [423], *Pyropia yezoensis* (formerly Porphyra yezoensis)(Rhodophyta), Coscinoderma mathewsi (Porifera), *Sargassum micranthum*, *Sargassum yezoense*, *Canistrocarpus cervicornis* (**Figure 24**), *Dictyota menstrualis*, *Ecklonia Kuromekurome*, *Ecklonia* spp. (Ochrophyta, Phaeophyceae) [424] have shown anticoagulantand anti-thrombotic properties. He et.al, al, 2019 reported that seaweed consumption may bea dietary predictor of elevated MEP, MiBP, and ∑DEHP concentrations among pregnantwomen [425]. Urolithiasis affects approximately 10% of the world population and is stronglyassociated with calcium oxalate (CaOx) crystals. Gomes *et al.*, 2019 reported anti-urolithiceffect of green seaweed *Caulerpa cupressoides* [426]. *Grateloupia elliptica* has the potentialto treat alopecia via inhibitory activity against *Malassezia furfur* (formerly *Pityrosporum ovale*) (Fungi, Basidiomycota) [427]. Strong fungus-inhibitory effects of *Ochtodes secundiramea* and *Laurencia dendroidea* (Rhodophyta) extracts were observed Banana and Papaya during storage [428]. Marine macroalgae are a promising source of diverse bioactive compounds with applications in the biocontrol of harmful cyanobacteria blooms [429].

Figure 21: *Bifurcaria bifurcate* (Source: APHOTOMARINE)

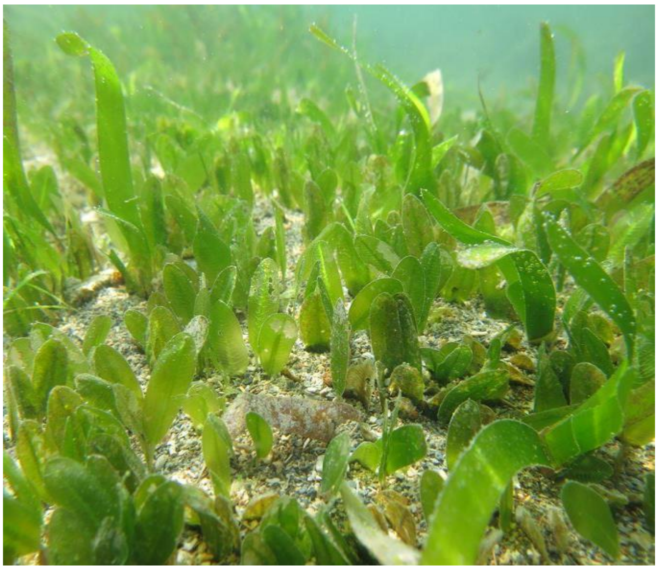

Figure 22: *Halophila ovalis*, Spoon Seagrass (Source: CoMBINe)

Figure 23: *Udotea flabellum* (Source: Insta Phenomenons)

Figure 24: ***Canistrocarpus cervicornis*** (Source: Backyard Nature)

Figure 25: ***Grateloupia elliptica*** (Source: Papago.naver.com)

Conclusion

Seaweeds are well-known for their exceptional capacity to accumulate essential minerals and trace elements needed for human nutrition, although their levels are commonly quite variable depending on their morphological features, environmental conditions, and geographic location. Food security, legislative measures to ensure monitoring and labeling of food products are needed. Being subject to environmental influences from their habitat, seaweeds also entail water-borne health risks such as organic pollutants, toxins, parasites, and heavy metals. Having in mind the serious environmental problems raised in coastal areas by urbanization and industrialization, the concentration of toxic elements in edible macroalgae is now a growing concern, mainly considering their increased consumption in a Western diet. Although many studies demonstrated their therapeutic value in various ailments, ~~but~~ most of them have been performed on experimental animals. Proper labelling is necessary along with instructions of the content, source and use. Furthermore, controlled human intervention studies with health-related end points to elucidate therapeutic efficacy are required.

Abbreviations

monoisobutyl phthalate (MiBP), monoethyl phthalate (MEP); The molar sum of MEHHP and MEOHP (∑DEHP); mono(2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP);World Economic Forum (WEF); Ischemic Heart Diseases (IHDs); Food and Agriculture Organization of the United Nations (UN-FAO); Gastric Emptying Breath Test (GEBT); Low and Middle Income Countries (LMICs); Conjugated Linoleic Acid (CLA); State of Food and Agriculture (SOFA); Uncoupling protein-1 (UCP-1); Hemoglobin A1c (HbA1c); extracellular signal–regulated kinases (ERK); Inflammatory bowel disease (IBD); Angiotensin Converting Enzyme (ACE); Osteoarthritis (OA); Cytochrome P450 1 (CYP1); Mitogen-Activated Protein Kinases (MAPK); Cyclooxygenase-2 (COX 2); Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/Akt); Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B cells (NF-κB)

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