

Therapeutic Values of Microalgae: A Comprehensive Review

Abdul Kader Mohiuddin *

**Dr. M. Nasirullah Memorial Trust, Tejgaon, Dhaka, Bangladesh.*

Received November 14, 2019; Accepted November 19, 2019; Published March 26, 2020

ABSTRACT

The global economic effect of the five driving chronic diseases — malignancy, diabetes, psychological instability, CVD and respiratory disease — could reach \$47 trillion throughout the following 20 years, as indicated by an examination by the World Economic Forum (WEF). As per the WHO, 80% of the total people principally those of developing countries depend on plant-inferred medicines for social insurance. The indicated efficacies of seaweed inferred phytochemicals are demonstrating incredible potential in obesity, T2DM, metabolic syndrome, CVD, IBD, sexual dysfunction and a few cancers. Hence, WHO, UN-FAO, UNICEF and governments have indicated a developing enthusiasm for these offbeat nourishments with well-being advancing impacts. Edible marine macro-algae (seaweed) are of intrigue in view of their incentive in nutrition and medicine. Seaweeds contain a few bioactive substances like polysaccharides, proteins, lipids, polyphenols and pigments, all of which may have useful wellbeing properties. People devour seaweed as nourishment in different structures: crude as salad and vegetable, pickle with sauce or with vinegar, relish or improved jams and furthermore cooked for vegetable soup. By cultivating seaweed, coastal people are getting an alternative livelihood just as propelling their lives. In 2005, world seaweed generation totaled 14.7 million tons which has dramatically increased (30.4 million tons) in 2015. The present market worth is almost \$6.5 billion and is anticipated to arrive at some \$9 billion in the seaweed global market by 2024. Aquaculture is perceived as the most practical methods for seaweed generation and records for around 27.3 million tons (over 90%) of global seaweed creation per annum. Asian nations created 80% for world markets where China alone delivers half of the complete interest. The best six seaweed delivering nations are China, Indonesia, Philippines, Korea and Japan.

Keywords: Seaweeds, Cancer prevention, Hyperglycemia management, Microalgae, Neuroprotection, Alimentary disorders

Abbreviations: MiBP: Monoisobutyl Phthalate; MEP: Monoethyl Phthalate; Σ DEHP: The Molar Sum of MEHHP and MEOHP; MEHP: Mono(2-Ethylhexyl) Phthalate; MEOHP: Mono(2-Ethyl-5-Oxoheptyl) Phthalate; WEF: World Economic Forum; IHDs: Ischemic Heart Diseases; UN-FAO: Food and Agriculture Organization of the United Nations; GEBT: Gastric Emptying Breath Test; LMICs: Low and Middle Income Countries; CLA: Conjugated Linoleic Acid; SOFA: State of Food and Agriculture; UCP-1: Uncoupling Protein-1; HbA1c: Hemoglobin A1c; ERK: Extracellular Signal-Regulated Kinases; IBD: Inflammatory Bowel Disease; ACE: Angiotensin Converting Enzyme; OA: Osteoarthritis; CYP1: Cytochrome P450 1; MAPK: Mitogen-Activated Protein Kinases; COX 2: Cyclooxygenase-2; PI3K/AktV: Phosphatidylinositol 3-Kinase/Protein Kinase B; NF- κ B: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells

INTRODUCTION

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 (**Figure 1**).

Corresponding author: Abdul Kader Mohiuddin, Secretary and Treasurer, Dr. M. Nasirullah Memorial Trust, Tejgaon, Dhaka, Bangladesh, Tel: +8801716477485; E-mail: trymohi@gmail.com

Citation: Mohiuddin AK. (2020) Therapeutic Values of Microalgae: A Comprehensive Review. J Pharm Drug Res, 3(2): 276-310.

Copyright: ©2020 Mohiuddin AK. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



Figure 1. Seaweed farming.

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. [8] reported Fucoxanthin powder developed from microalga *Phaeodactylum tricornutum* (Bacillariophyta) plus CLA or Xanthigen improved lipid metabolism, reduced body weight gain and adipose tissue. Individually, fucoxanthin lowers glycated hemoglobin, especially in healthy subjects with a certain UCP1 genotype [9]. Mendez et al. [10] reported anti-obesogenic potential of seaweed dulse (*Palmaria palmata*) (Rhodophyta) (**Figure 2**) in high-fat fed mice. Seca et al. [11] suggested that small peptides from seaweed may possess bioactivity, for example, of relevance for BP regulation. Yang et al. [12] reported Fucoidan A2 from the brown seaweed *Ascophyllum nodosum* (Ochrophyta, Phaeophyceae) (**Figure 3**) lowers lipid by improving reverse cholesterol transport in mice. Sørensen et al. [13] reported

improved HbA1C and lipid profile with *Saccharina latissima* (Ochrophyta, Phaeophyceae) or sugar kelp (**Figure 4**) in mice. 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. [20] reported *Fucus vesiculosus* (Ochrophyta, Phaeophyceae) (**Figure 5**) phlorotannin-rich extracts have significant effect on α -glucosidase, α -amylase and pancreatic lipase. 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. 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 clathrate*), *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], *Fushitsunagia catenata* (formerly *Lomentaria catenata*), *Lithophyllum okamurae*, *Ahnfeltiopsis flabelliformis* (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. 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, hypolipemic and antiatherogenic properties [31-40]. Moreover, studies also support seaweed-induced effects of postprandial

lipoproteinemia [41-43], postprandial hyperglycemia [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 palmate*.

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 AND 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 death in 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. *Egredia 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 diesters are the green microalgae (*Hematococcus 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* ssp. *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* ssp. *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- κ B in LLC [161]. *U. pinnatifida* was found to show average antitumor and superior efficacy against LLC in the review of Misra et al. [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. [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), *Sargassum muticum* (polyphenol), *Pyropia dentata* (formerly *Porphyra dentata*) (sterol fraction), *Cymopolia barbata* (CYP1 inhibitors), *Agarophyton tenuistipitatum* (formerly *Gracilaria tenuistipitata*) *Gracilaria termistipitata* was found to be effective in breast cancer studies [166]. High Urokinase-type plasminogen activator receptor (uPAR) expression predicts for more aggressive disease in several cancer types [167], dietary seaweed may help lowering breast cancer incidence by diminishing levels of uPAR [168]. The tropical edible red seaweed *Kappaphycus alvarezii* (formerly *Eucheuma cottonii*) (**Figure 10**) is rich in polyphenols that exhibited strong anticancer effect with enzyme modulating properties [169]. Jazzara et al. [170] concluded that λ -carrageenan (sulfated galactans found in certain red seaweeds) could be a promising bioactive polymer, 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], other seaweed 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 have 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

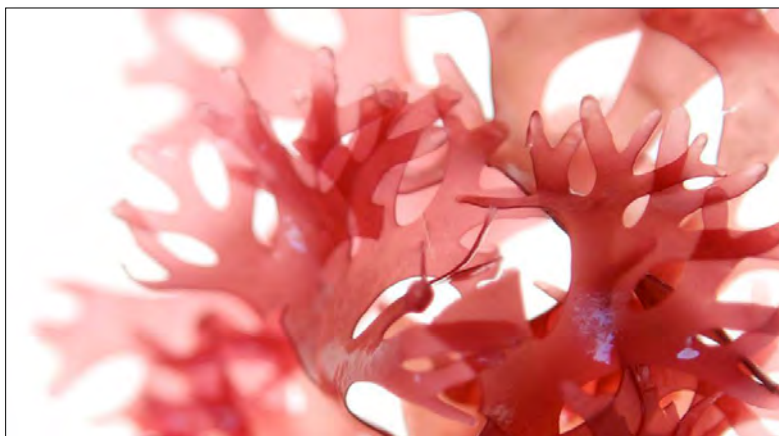


Figure 7. *Haematococcus pluvialis*.

Source: VERYMWL, Thailand



Figure 8. *Saccharina japonica* (formerly *Laminaria japonica*).

Source: TCM Herbs



Figure 9. *Sargassum* sp.

Source: POND5



Figure 10. *Kappaphycus alvarezii* (formerly *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. reported that marine algae inhibit pro-inflammatory enzymes such as COX-2 and iNOS, modulate MAPK pathways, and activate NK-kB [269]. *Neorhodomela aculeata*, *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 *Bryothamnion 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

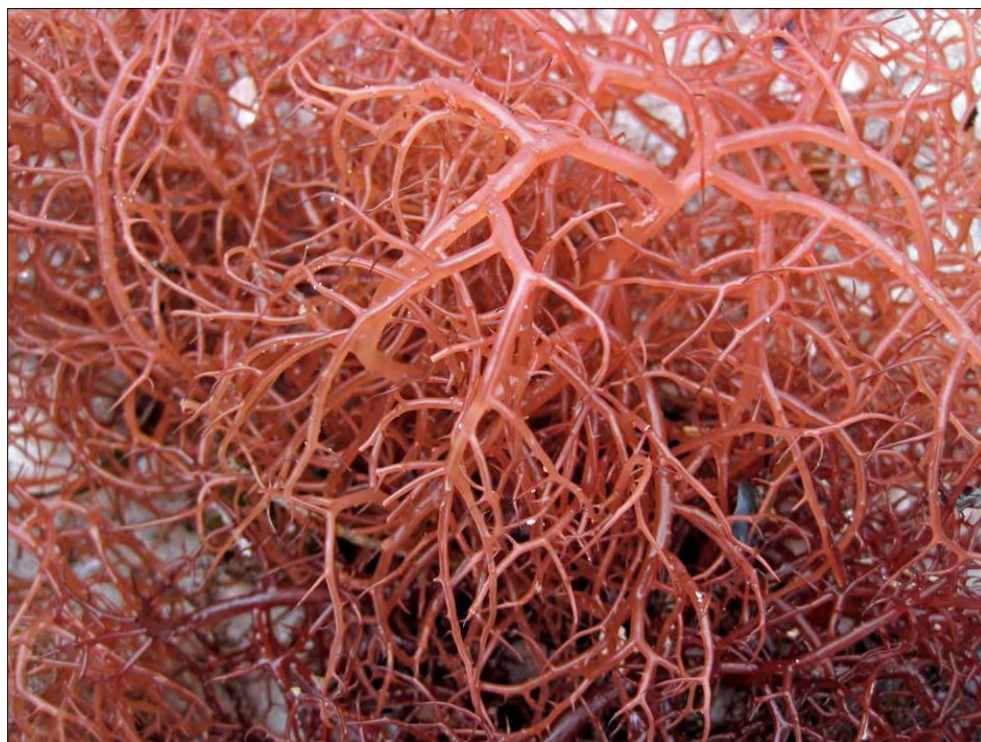


Figure 12. *Gracilaria tikvahiae* - Red seaweed

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]. Nalginatate has been used in the treatment of heartburn and GERD, although ESPGHAN/NASPGHAN Guidelines do not recommend its 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 vesiculosus* (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

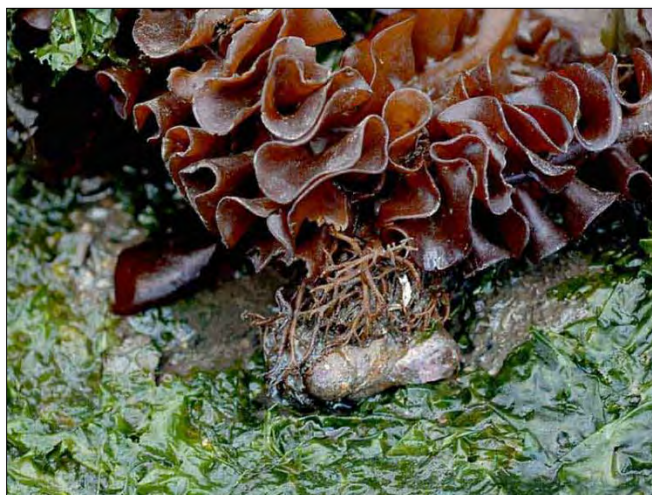


Figure 16. *Undaria pinnatifida*.

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 seaweed is 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]. 1 g 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 spongiosum*, *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 and Chlorophyta [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], *Briareum excavatum* (Octocoral) [386], *Caulerpa racemosae* (Chlorophyta) [387], *Sargassum hemiphyllum* (Ochrophyta, Phaeophyceae) [388], *Laurencia obtusa* (Rhodophyta) [389], *Caulerpa kempfii* [390], *Caulerpa cupressoides* (Chlorophyta) [391] are reported for their analgesic and anti-inflammatory properties.

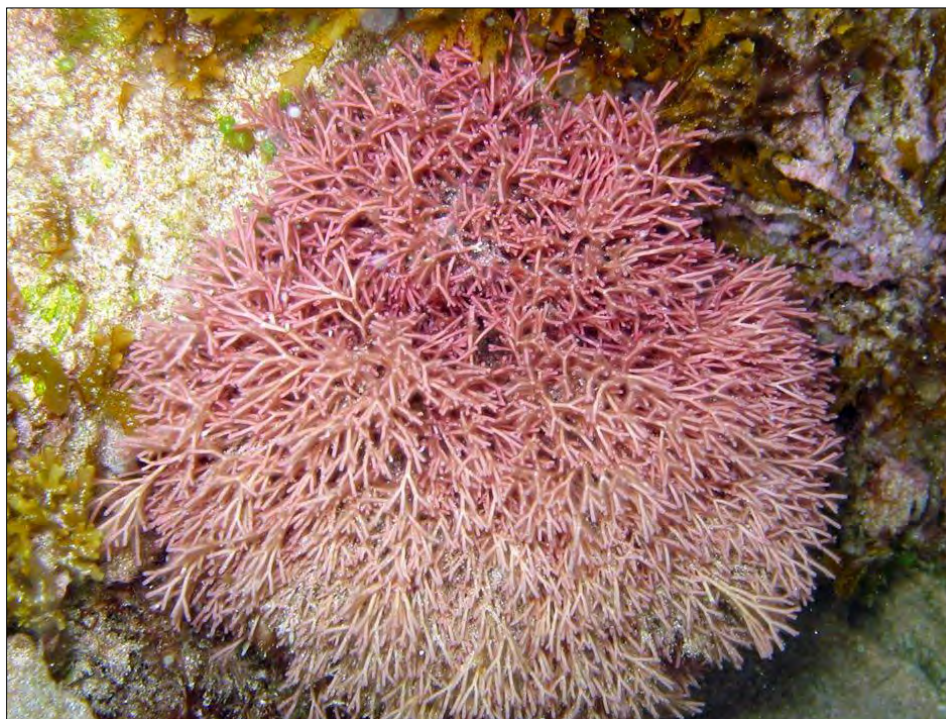


Figure 17. *Dichotomaria obtusata*, Tubular Thicket Algae.

Source: 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 and estimated to cause 10 million deaths annually by 2050 with global economic loss \$100 trillion [392-394]. Lu et al. reported *Saccharina japonica* (formerly *Laminaria japonica*), *Sargassum* (Ochrophyta, Phaeophyceae), *Gracilaria* sp. and *Pyropia dentata* (formerly *Porphyra dentata*) (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. [396] 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 (Table 1).

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

Red Seaweed	Organisms
<i>Alsidium corallinum</i>	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Staphylococcus aureus</i>
<i>Ceramium rubrum</i>	<i>E. coli</i> , <i>Enterococcus faecalis</i> , <i>S. aureus</i>
<i>Ceramium virgatum</i>	<i>Salmonella enteritidis</i> , <i>E. coli</i> , <i>Listeria monocytogenes</i> , <i>Bacillus cereus</i>
<i>Chondrocanthus acicularis</i>	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>S. aureus</i>
<i>Chondracanthus canaliculatus</i>	<i>S. aureus</i> , <i>Streptococcus pyogenes</i>
<i>Chondrus crispus</i>	<i>L. monocytogenes</i> , <i>Salmonella abony</i> , <i>E. faecalis</i> , <i>P. aeruginosa</i>
<i>C. crispus</i>	<i>Pseudoalteromonas elyakovii</i> , <i>Vibrio aestuarianus</i> , <i>Polaribacter irgensii</i> , <i>Halomonas marina</i> , <i>Shewanella putrefaciens</i>
<i>Ellisolandia elongata</i> (formerly <i>Corallina elongataelongata</i>)	<i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>Salmonella typhi</i> , <i>K. pneumoniae</i> , <i>Candida albicans</i>
<i>Gelidium attenatum</i>	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>S. aureus</i>
<i>Gelidium micropterum</i>	<i>V. parahaemolyticus</i> , <i>V. alcaligenes</i>
<i>Gelidium pulchellum</i>	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>
<i>Gelidium robustum</i>	<i>S. aureus</i> , <i>S. pyogenes</i>
<i>Gelidium spinulosum</i>	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>
<i>Gracilaria dura</i>	<i>V. ordalii</i> , <i>V. alginolyticus</i>
<i>Gracilaria gracilis</i>	<i>V. salmonicida</i>
<i>Grateloupia livida</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i>
<i>Gracilaria ornata</i>	<i>E. coli</i>
<i>Gracilaria subsecundata</i>	<i>S. aureus</i> , <i>S. pyogenes</i>
Green Seaweed	Organisms
<i>Boodlea composita</i>	<i>V. harveyi</i> , <i>V. alginolyticus</i> , <i>V. vulnificus</i> , <i>V. parahaemolyticus</i> , <i>V. alcaligenes</i>
<i>Bryopsis pennata</i>	<i>V. vulnificus</i> , <i>V. parahemolyticus</i>
<i>Caulerpa lentillifera</i>	<i>E. coli</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus</i> sp., <i>Salmonella</i> sp.
<i>Caulerpa parvula</i>	<i>V. vulnificus</i> , <i>V. alcaligenes</i>
<i>Caulerpa racemosa</i>	<i>E. coli</i> , <i>S. aureus</i> , <i>Streptococcus</i> sp., <i>Salmonella</i> sp.

<i>Chaetomorpha aerea</i>	<i>Bacillus subtilis</i> , <i>Micrococcus luteus</i> , <i>S. aureus</i>
<i>Chaetomorpha linum</i>	<i>V. ordalii</i> , <i>V. vulnificus</i>
<i>Cladophora albida</i>	<i>V. harveyi</i> , <i>V. alginolyticus</i> , <i>V. vulnificus</i> , <i>V. parahemolyticus</i> , <i>V. alcaligenes</i>
<i>Cladophora glomerata</i>	<i>V. fischeri</i> , <i>V. vulnificus</i> , <i>V. anguillarum</i> , <i>V. parahemolyticus</i>
Brown Seaweed	Organisms
<i>Chnoospora implexa</i>	<i>S. aureus</i> , <i>S. pyogenes</i>
<i>Cladophora rupestris</i>	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>V. harveyi</i> , <i>V. parahemolyticus</i> , <i>V. alginolyticus</i>
<i>C. rupestris</i>	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>V. harveyi</i> , <i>V. parahemolyticus</i> , <i>V. alginolyticus</i>
<i>C. rupestris</i>	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>V. harveyi</i> , <i>V. parahemolyticus</i>
<i>Colpomenia sinuosa</i>	<i>S. aureus</i> , <i>S. pyogenes</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>S. typhi</i> , <i>K. pneumoniae</i> , <i>C. albicans</i>
<i>Colpomenia tuberculata</i>	<i>S. aureus</i> , <i>S. pyogenes</i>
<i>Cystoseira osmundacea</i>	<i>S. pyogenes</i>
<i>Cystoseira trinodis</i>	<i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i>
<i>Dictyopteris delicatula</i>	<i>S. aureus</i> , <i>S. pyogenes</i>
<i>Dictyopteris undulata</i>	<i>S. aureus</i> , <i>S. pyogenes</i>
<i>Dictyota dichotoma</i>	<i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i>
<i>Dictyota flabellata</i>	<i>S. aureus</i> , <i>S. pyogenes</i>
<i>Dictyota indica</i>	<i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i>
<i>Dictyota sp.</i>	<i>S. aureus</i> , <i>Enterococcus faecalis</i> , <i>P. aeruginosa</i>
<i>Ecklonia bicyclis</i> (formerly <i>Eisenia bicyclis</i>)	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>Propionibacterium acnes</i>

OTHER HEALTH ISSUES

Walsh et al. reported osteogenic potential of brown seaweeds *Laminaria digitata* and *Ascophyllum nodosum* [398]. Seaweed contains several compounds with antioxidant properties (phlorotannins, pigments, tocopherols, flavonoids, polyphenols and polysaccharides) [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 bifurcata* (**Figure 21**) (diterpenes eleanolone and eleanonal) [402], *Cystoseira* spp. (phenolic constituents) [119], *Sargassum siliquastrum* (Ochrophyta, Phaeophyceae) (phenolic compounds, 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 peltatopeltate* (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 other medicinal effects are mainly due to presence of these antioxidants. Mesripour et al. [415] reported antidepressant effects of *Sargassum plagiophyllum*. *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 reduce libido [416]. However, red algae (especially sea moss/*Gracilaria* spp.), *Hypnea musciformis* (Vermifuge), *Monostroma nitidum* (formerly *Porphyra crispata*) are known to have aphrodisiac properties [417-419]. Thrombotic diseases are reported to contribute to 30% early deaths globally [420]. *Ulva rigida* [421], *Udotea flabellum* (Chlorophyta) (**Figure 23**) [422], ulvans and their oligosaccharides [380], *Nemacystus decipiens*, *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 Kuromekurume*, *Ecklonia* spp. (Ochrophyta, Phaeophyceae) [424] have shown anticoagulant and anti-thrombotic properties. He et

al. reported that seaweed consumption may be a dietary predictor of elevated MEP, MiBP and Σ DEHP concentrations among pregnant women [425]. Urolithiasis affects approximately 10% of the world population and is strongly associated with calcium oxalate (CaOx) crystals. Gomes et al. reported anti-urolithic effect of green seaweed *Caulerpa cupressoides* [426]. *Grateloupia elliptica* has the potential to 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

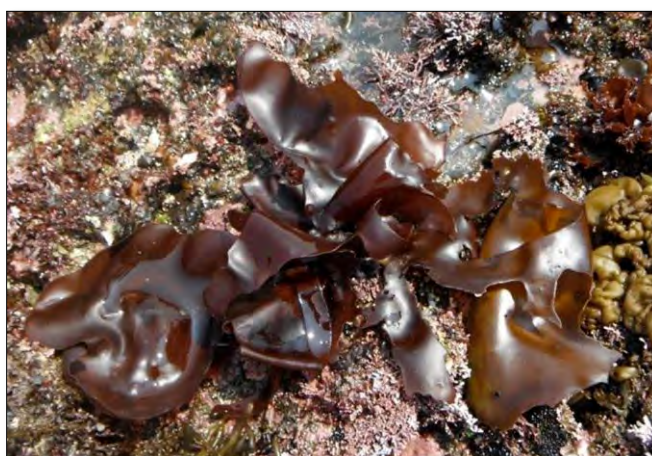


Figure 25. *Grateloupia elliptica*.

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 labeling 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.

FINANCIAL DISCLOSURE OR FUNDING

N/A

CONFLICT OF INTEREST

The author declares that he has no competing interests.

INFORMED CONSENT

N/A

AUTHOR CONTRIBUTIONS

N/A

REFERENCES

1. Ma RCW, Schmidt MI, Tam WH, McIntyre HD, Catalano PM (2016) Clinical management of pregnancy in the obese mother: Before conception, during pregnancy and postpartum *Lancet Diabetes Endocrinol* 4: 1037-1049.
2. Panuganti KK, Gossman WG (2019) Obesity StatPearls Treasure Island (FL). StatPearls Publishing. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459357/>
3. Dagne S, Gelaw YA, Abebe Z, Wassie MM (2019) Factors associated with overweight and obesity among adults in northeast Ethiopia: A cross-sectional study *Diabetes Metab Syndr Obes* 12: 391-399.
4. Wan-Loy C, Siew-Moi P (2016) Marine algae as a potential source for anti-obesity agents. *Drugs* 14 pii: E222.
5. Chater PI, Wilcox M, Cherry P, Herford A, Mustar S, et al. (2016) Inhibitory activity of extracts of Hebridean brown seaweeds on lipase activity *J Appl Phycol* 28: 1303-1313.
6. Tran VC, Cho SY, Kwon J, Kim D (2019) Alginate oligosaccharide (AOS) improves immuno-metabolic systems by inhibiting STOML2 overexpression in high-fat-diet-induced obese zebrafish *Food Funct* 10: 4636-4648.
7. Wang X, Liu F, Gao Y, Xue CH, Li RW, et al. (2018) Transcriptome analysis revealed anti-obesity effects of the sodium alginate in high-fat diet induced obese mice. *Int J Biol Macromol* 115: 861-870.
8. Koo SY, Hwang JH, Yang SH, Um JI, Hong KW, et al. (2019) Anti-obesity effect of standardized extract of microalga *Phaeodactylum tricornutum* containing fucoxanthin. *Mar Drugs* 17 pii: E311.
9. Mikami N, Hosokawa M, Miyashita K, Sohma H, Ito YM, et al. (2017) Reduction of HbA1c levels by fucoxanthin-enriched akamoku oil possibly involves the thrifty allele of uncoupling protein 1 (UCP1): A randomised controlled trial in normal-weight and obese Japanese adults *J Nutr Sci* 6: e5.
10. Mendez R, Miranda C, Armour C, Sharpton T, Stevens JF, et al. (2019) Anti-obesogenic potential of seaweed dulse (*Palmaria palmata*) in high-fat fed C57BL/6 J mice P21-014-19. *Curr Dev Nutr* 3.
11. Seca AML, Pinto DCGA (2018) Overview on the antihypertensive and anti-obesity effects of secondary metabolites from seaweeds. *Mar Drugs* 16 pii: E237.
12. Yang Z, Liu G, Wang Y, Yin J, Wang J, et al. (2019) Fucoidan A2 from the brown seaweed *Ascophyllum nodosum* lowers lipid by improving reverse cholesterol transport in C57BL/6J mice fed a high-fat diet. *J Agric Food Chem* 67: 5782-5791.
13. Sørensen LE, Jeppesen PB, Christiansen CB, Hermansen K, Gregersen S (2019) Nordic seaweed and diabetes prevention: Exploratory studies in KK-Ay mice. *Nutrients* 11 pii: E1435.
14. Wright CM, Bezabhe W, Fitton JH, Stringer DN, Bereznicki LRE, et al. (2019) Effect of a fucoidan extract on insulin resistance and cardiometabolic markers in obese, non-diabetic subjects: A randomized, controlled trial. *J Altern Complement Med* 25: 346-352.
15. Ahn JH, Shin MC, Kim DW, Kim H, Song M, et al. (2019) Antioxidant properties of fucoidan alleviate acceleration and exacerbation of hippocampal neuronal death following transient global cerebral ischemia in high-fat diet-induced obese gerbils. *Int J Mol Sci* 20 pii: E554.

16. Wang Y, Xing M, Cao Q, Ji A, Liang H, et al. (2019) Biological activities of fucoidan and the factors mediating its therapeutic effects: A review of recent studies. *Mar Drugs* 17 pii: E183.
17. Kim MJ, Jeon J, Lee JS (2014) Fucoidan prevents high-fat diet-induced obesity in animals by suppression of fat accumulation. *Phytother Res* 28: 137-143.
18. Sudirman S, Ong AD, Chang HW, Kong ZL (2018) Effect of fucoidan on anterior cruciate ligament transection and medial meniscectomy induced osteoarthritis in high-fat diet-induced obese rats. *Nutrients* 10 pii: E686.
19. Oliveira RM, Câmara RBG, Monte JFS, Viana RLS, Melo KRT, et al. (2018) Commercial fucoidans from *Fucus vesiculosus* can be grouped into anti-adipogenic and adipogenic agents. *Mar Drugs* 16 pii: E193.
20. Catarino MD, Silva AMS, Mateus N, Cardoso SM (2019) Optimization of phlorotannins extraction from *Fucus vesiculosus* and Evaluation of Their Potential to Prevent Metabolic Disorders. *Mar Drugs* 17 pii: E162.
21. Catarino MD, Silva AMS, Cardoso SM (2017) Fucaceae: A source of bioactive phlorotannins. *Int J Mol Sci* 18 pii: E1327.
22. Sun S, Xu X, Sun X, Zhang X, Chen X, et al. (2019) Preparation and identification of ACE inhibitory peptides from the marine macroalga *Ulva intestinalis*. *Mar Drugs* 17 pii: E179.
23. Nagappan H, Pee PP, Kee SHY, Ow JT, Yan SW, et al. (2017) Malaysian brown seaweeds *Sargassum siliculosum* and *Sargassum polycystum*: Low density lipoprotein (LDL) oxidation, angiotensin converting enzyme (ACE), α -amylase and α -glucosidase inhibition activities. *Food Res Int* 99: 950-958.
24. Paiva L, Lima E, Neto AI, Baptista J (2017) Angiotensin I-converting enzyme (ACE) inhibitory activity, antioxidant properties, phenolic content and amino acid profiles of *Fucus spiralis* L. protein hydrolysate fractions. *Mar Drugs* 15 pii: E311.
25. Seca AML, Pinto DCGA (2018) Overview on the antihypertensive and anti-obesity effects of secondary metabolites from seaweeds. *Mar Drugs* 16 pii: E237.
26. Pangestuti R, Kim SK (2017) Bioactive peptide of marine origin for the prevention and treatment of non-communicable diseases. *Mar Drugs* 15 pii: E67.
27. Collins KG, Fitzgerald GF, Stanton C, Ross RP (2016) Looking beyond the terrestrial: The potential of seaweed derived bio actives to treat non-communicable diseases. *Mar Drugs* 14 pii: E60.
28. Gómez-Guzmán M, Rodríguez-Nogales A, Algieri F, Gálvez J (2018) Potential role of seaweed polyphenols in cardiovascular-associated disorders. *Mar Drugs* 16 pii: E250.
29. Majumder K, Wu J (2014) Molecular targets of antihypertensive peptides: Understanding the mechanisms of action based on the pathophysiology of hypertension. *Int J Mol Sci* 16: 256-283.
30. Kammoun I, Ben Salah H, Ben Saad H, Cherif B, Droguet M, et al. (2018) Hypolipidemic and cardioprotective effects of *Ulva lactuca* ethanolic extract in hypercholesterolemic mice. *Arch Physiol Biochem* 124: 313-325.
31. Pengzhan Y, Ning L, Xiguang L, Gefei Z, Quanbin Z, et al. (2003) Anti-hyperlipidemic effects of different molecular weight sulphated polysaccharides from *Ulva pertusa* (Chlorophyta). *Pharmacol Res* 48: 543-549.
32. Wang R, Paul VJ, Luesch H (2013) Seaweed extracts and unsaturated fatty acid constituents from the green alga *Ulva lactuca* as activators of the cytoprotective Nrf2-ARE pathway. *Free Radic Biol Med* 57: 141-153.
33. Yu Y, Li Y, Du C, Mou H, Wang P (2017) Compositional and structural characteristics of sulphated polysaccharide from *Enteromorpha prolifera*. *Carbohydr Polym* 165: 221-228.
34. Sharifuddin Y, Chin YX, Lim PE, Phang SM (2015) Potential bioactive compounds from seaweed for diabetes management. *Mar Drugs* 13: 5447-5491.
35. Tair ZI, Bensalah F, Boukortt F (2018) Effect of green alga *Ulva lactuca* polysaccharides supplementation on blood pressure and on atherogenic risk factors, in rats fed a high fat diet. *Ann Cardiol Angeiol (Paris)* 67: 133-140.
36. Lauritano C, Ianora A (2016) Marine organisms with anti-diabetes properties. *Mar Drugs* 14 pii: E220.
37. Mohapatra L, Bhattamishra SK, Panigrahy R, Parida S, Pati P (2016) Anti-diabetic effect of *Sargassum wightii* and *Ulva fasciata* in high fat diet and multi low dose streptozotocin induced type 2 diabetic mice. *UK J Pharm Biosci* 4: 13-23.
38. Celikler S, Tas S, Vatan O, Ziyank-Ayvalik S, Yildiz G, Bilaloglu R (2009) Anti-hyperglycemic and anti-genotoxic potential of *Ulva rigida* ethanolic extract in the experimental diabetes mellitus. *Food Chem Toxicol* 47: 1837-1840.
39. Hassan S, El-Twab SA, Hetta M, Mahmoud B (2011) Improvement of lipid profile and antioxidant of hypercholesterolemic albino rats by polysaccharides extracted from the green alga *Ulva lactuca* Linnaeus. *Saudi J Biol Sci* 18: 333-340.
40. BelHadj S, Hentati O, Elfeki A, Hamden K (2013) Inhibitory activities of *Ulva lactuca* polysaccharides on

- digestive enzymes related to diabetes and obesity. Arch Physiol Biochem 119: 81-87.
41. Bocanegra A, Bastida S, Benedí J, Nus M, Sánchez-Montero JM, et al. (2009) Effect of seaweed and cholesterol-enriched diets on postprandial lipoproteinemia in rats. Br J Nutr 102: 1728-1739.
 42. Schultz Moreira AR, Olivero-David R, Vázquez-Velasco M, González-Torres L, Benedí J, et al. (2014) Protective effects of sea spaghetti-enriched restructured pork against dietary cholesterol: Effects on aryl esterase and lipoprotein profile and composition of growing rats. J Med Food 17: 921-928.
 43. Nasir M, Saeidnia S, Mashinchian-Moradi A, Gohari AR (2011) Sterols from the red algae, *Gracilaria salicornia* and *Hypnea flagelliformis*, from Persian Gulf. Pharmacogn Mag 7: 97-100.
 44. Gabbia D, Dall'Acqua S, Di Gangi IM, Bogialli S, Caputi V, et al. (2017) The phytocomplex from *Fucus vesiculosus* and *Ascophyllum nodosum* controls postprandial plasma glucose levels: An *in vitro* and *in vivo* study in a mouse model of NASH. Mar Drugs 15 pii: E41.
 45. Kim MS, Kim JY, Choi WH, Lee SS (2008) Effects of seaweed supplementation on blood glucose concentration, lipid profile and antioxidant enzyme activities in patients with type 2 diabetes mellitus. Nutr Res Pract Summer 2: 62-67.
 46. Murray M, Dordevic AL, Ryan L, Bonham MP (2018) The impact of a single dose of a polyphenol-rich seaweed extract on postprandial glycemic control in healthy adults: A randomised cross-over trial. Nutrients 10 pii: E270.
 47. Tanemura Y, Yamanaka-Okumura H, Sakuma M, Nii Y, Taketani Y, et al. (2014) Effects of the intake of *Undaria pinnatifida* (Wakame) and its sporophylls (Mekabu) on postprandial glucose and insulin metabolism. J Med Invest 61: 291-297.
 48. Haskell-Ramsay CF, Jackson PA, Dodd FL, Forster JS, Bérubé J, et al. (2018) Acute post-prandial cognitive effects of brown seaweed extract in humans. Nutrients 10 pii: E85.
 49. Cherry P, O'Hara C, Magee PJ, McSorley EM, Allsopp PJ (2019) Risks and benefits of consuming edible seaweeds. Nutr Rev 77: 307-329.
 50. Gotama TL, Husni A, Ustadi (2018) Anti-diabetic activity of *Sargassum hystris* extracts in streptozotocin-induced diabetic rats. Prev Nutr Food Sci 23: 189-195.
 51. Lee CW, Han JS (2012) Hypoglycemic effect of *Sargassum ringgoldianum* extract in STZ-induced diabetic mice. Prev Nutr Food 17: 8-13.
 52. Yang HW, Fernando KHN, Oh JY, Li X, Jeon YJ, et al. (2019) Anti-obesity and anti-diabetic effects of *Ishige okamurae*. Mar Drugs 17 pii: E202.
 53. Murray M, Dordevic AL, Ryan L, Bonham MP (2019) A single-dose of a polyphenol-rich *Fucus vesiculosus* extract is insufficient to blunt the elevated postprandial blood glucose responses exhibited by healthy adults in the evening: A randomised crossover trial. Antioxidants (Basel) 8 pii: E49.
 54. Coe S, Ryan L (2016) Impact of polyphenol-rich sources on acute postprandial glycemia: A systematic review. J Nutr Sci 5: e24.
 55. Murugan AC, Karim MR, Yusoff MB, Tan SH, Asras MF, et al. (2015) New insights into seaweed polyphenols on glucose homeostasis. Pharm Biol 53: 1087-1097.
 56. Yang Z, Yin J, Wang Y, Wang J, Xia B, et al. (2019) The fucoidan A3 from the seaweed *Ascophyllum nodosum* enhances RCT-related genes expression in hyperlipidemic C57BL/6J mice. Int J Biol Macromol 134: 759-769.
 57. Kamunde C, Sappal R, Melegy TM (2019) Brown seaweed (AquaArom) supplementation increases food intake and improves growth, antioxidant status and resistance to temperature stress in Atlantic salmon, *Salmo salar*. PLoS One 14: e0219792.
 58. Yang Z, Liu G, Wang Y, Yin J, Wang J, et al. (2019) Fucoidan A2 from the brown seaweed *Ascophyllum nodosum* lowers lipid by improving reverse cholesterol transport in C57BL/6J mice fed a high-fat diet. J Agric Food Chem 67: 5782-5791.
 59. Yone Y, Furuichi M, Urano K (1986) Effects of wakame *Undaria pinnatifida* and *Ascophyllum nodosum* on absorption of dietary nutrients and blood sugar and plasma free amino- N levels of red sea bream. Nippon Suisan Gakkaishi 52: 1817.
 60. Dy Peñafiorida V, Golez NV, Peikflorida VD, Golez NV (1996) Use of seaweed meals from *Kappaphycus alvarezii* and *Gracilaria heteroclada* as binders in diets for juvenile shrimp *Penaeus monodon*. Aquaculture 143: 393.
 61. Nakagawa H (1997) Effect of dietary algae on improvement of lipid metabolism in fish. Biomed Pharmacother 51: 345-348.
 62. Gille A, Stojnic B, Derwenskus F, Trautmann A, Schmid-Staiger U, et al. (2019) A lipophilic fucoxanthin-rich *Phaeodactylum tricornutum* extract ameliorates effects of diet-induced obesity in C57BL/6J mice. Nutrients 11pii: E796.

63. Jeon SM, Kim HJ, Woo MN, Lee MK, Shin YC, et al. (2010) Fucoxanthin-rich seaweed extract suppresses body weight gain and improves lipid metabolism in high-fat-fed C57BL/6J mice. *Biotechnol J* 5: 961-969.
64. Chin YX, Mi Y, Cao WX, Lim PE, Xue CH, et al. (2019) A pilot study on anti-obesity mechanisms of *Kappaphycus alvarezii*: The role of native κ-carrageenan and the leftover sans-carrageenan fraction. *Nutrients* 11 pii: E1133.
65. Ha AW, Kim WK (2013) The effect of fucoxanthin rich powder on the lipid metabolism in rats with a high fat diet. *Nutr Res Pract* 7: 287-293.
66. Patil NP, Le V, Sligar AD, Mei L, Chavarria D, et al. (2018) Algal polysaccharides as therapeutic agents for atherosclerosis. *Front Cardiovasc* 5: 153.
67. Wan X, Li T, Liu D, Chen Y, Liu Y, et al. (2018) Effect of marine microalga *Chlorella pyrenoidosa* ethanol extract on lipid metabolism and gut microbiota composition in high-fat diet-fed rats. *Mar Drugs* 16 pii: E498.
68. Li TT, Liu YY, Wan XZ, Huang ZR, Liu B, et al. (2018) Regulatory efficacy of the polyunsaturated fatty acids from microalgae *Spirulina platensis* on lipid metabolism and gut microbiota in high-fat diet rats. *Int J Mol Sci* 19 pii: E3075.
69. Yin J, Wang J, Li F, Yang Z, Yang X, et al. (2019) The fucoidan from the brown seaweed *Ascophyllum nodosum* ameliorates atherosclerosis in apolipoprotein E-deficient mice. *Food Funct* 10: 5124-5139.
70. Shijo Y, Maruyama C, Nakamura E, Nakano R, Shima M, et al. (2019) Japan diet intake changes serum phospholipid fatty acid compositions in middle-aged men: A pilot study. *J Atheroscler Thromb* 26: 3-13.
71. Zhao B, Cui Y, Fan X, Qi P, Liu C, et al. (2019) Anti-obesity effects of *Spirulina platensis* protein hydrolysate by modulating brain-liver axis in high-fat diet fed mice. *PLoS One* 14: e0218543.
72. Coué M, Tesse A, Falewée J, Aguesse A, Croyal M, et al. (2019) Spirulina liquid extract protects against fibrosis related to non-alcoholic steatohepatitis and increases ursodeoxycholic acid. *Nutrients* 11 pii: E194.
73. Huang H, Liao D, Pu R, Cui Y (2018) Quantifying the effects of spirulina supplementation on plasma lipid and glucose concentrations, body weight and blood pressure. *Diabetes Metab Syndr Obes* 11: 729-742.
74. Masuda K, Chitundu M (2019) Multiple micronutrient supplementation using *Spirulina platensis* and infant growth, morbidity and motor development: Evidence from a randomized trial in Zambia. *PLoS One* 14: e0211693.
75. Hu J, Li Y, Pakpour S, Wang S, Pan Z, et al. (2019) Dose effects of orally administered Spirulina suspension on colonic microbiota in healthy mice. *Front Cell Infect Microbiol* 9: 243.
76. Hernández-Lepe MA, Wall-Medrano A, López-Díaz JA, Juárez-Oropeza MA, Hernández-Torres RP, et al. (2019) Hypolipidemic effect of arthrospira (*Spirulina maxima*) supplementation and a systematic physical exercise program in overweight and obese men: A double-blind, randomized and crossover controlled trial. *Mar Drugs* 17 pii: E270.
77. Kim JY, Kwon YM, Kim IS, Kim JA, Yu DY, et al. (2018) Effects of the brown seaweed *Laminaria japonica* supplementation on serum concentrations of IgG, triglycerides, cholesterol and intestinal microbiota composition in rats. *Front Nutr* 5: 23.
78. Barros-Gomes JAC, Nascimento DLA, Silveira ACR, Silva RK, Gomes DL, et al. (2018) *In vivo* evaluation of the antioxidant activity and protective action of the seaweed *Gracilaria birdiae*. *Oxid Med Cell Longev* 2018: 9354296.
79. López-Rios L, Vega T, Chirino R, Jung JC, Davis B, et al. (2018) Toxicological assessment of Xanthigen® nutraceutical extract combination: Mutagenicity, genotoxicity and oral toxicity. *Toxicol Rep* 5: 1021-1031.
80. Wanyonyi S, du Preez R, Brown L, Paul NA, Panchal SK (2017) *Kappaphycus alvarezii* as a food supplement prevents diet-induced metabolic syndrome in rats. *Nutrients* 9 pii: E1261.
81. Mikami N, Hosokawa M, Miyashita K, Sohma H, Ito YM, et al. (2017) Reduction of HbA1c levels by fucoxanthin-enriched akamoku oil possibly involves the thrifty allele of uncoupling protein 1 (UCP1): A randomised controlled trial in normal-weight and obese Japanese adults. *J Nutr Sci* 6: e5.
82. Seo YJ, Lee K, Chei S, Jeon YJ, Lee BY (2019) *Ishige okamurae* extract ameliorates the hyperglycemia and body weight gain of db/db mice through regulation of the PI3K/Akt pathway and thermogenic factors by FGF21. *Mar Drugs* 17 pii: E407.
83. Sakai C, Abe S, Kouzuki M, Shimohiro H, Ota Y, et al. (2019) A randomized placebo-controlled trial of an oral preparation of high molecular weight fucoidan in patients with type 2 diabetes with evaluation of taste sensitivity. *Yonago Acta Med* 62: 14-23.
84. Choi J, Kim KJ, Koh EJ, Lee BY (2018) *Gelidium elegans* extract ameliorates type 2 diabetes via regulation of MAPK and PI3K/Akt signalling. *Nutrients* 10 pii: E51.

85. Maeda H, Fukuda S, Izumi H, Saga N (2018) Anti-oxidant and fucoxanthin contents of brown alga Ishimozuku (*Sphaerotrichia divaricata*) from the west coast of Aomori, Japan. Mar Drugs 16 pii: E255.
86. McMacken M, Shah S (2017) A plant-based diet for the prevention and treatment of type 2 diabetes J Geriatr 14: 342-354.
87. Takahashi K, Kamada C, Yoshimura H, Okumura R, Iimuro S, et al. (2012) Japanese elderly diabetes intervention trial study group effects of total and green vegetable intakes on glycated hemoglobin A1c and triglycerides in elderly patients with type 2 diabetes mellitus: The Japanese Elderly Intervention Trial. Geriatr Gerontol Int 12: 50-58.
88. Motshakeri M, Ebrahimi M, Goh YM, Matanjun P, Mohamed S (2013) *Sargassum polycystum* reduces hyperglycemia, dyslipidemia and oxidative stress via increasing insulin sensitivity in a rat model of type 2 diabetes. J Sci Food Agric 93: 1772-1778.
89. Motshakeri M, Ebrahimi M, Goh YM, Othman HH, Hair-Bejo M, et al. (2014) Effects of brown seaweed (*Sargassum polycystum*) extracts on kidney, liver, and pancreas of type 2 diabetic rat model. Evid Based Complement Altern Med 2014: 379407.
90. Johnson J (2018) What are the benefits of seaweed? MedicalNewsToday, Accessed on: 6 December.
91. Son M, Oh S, Lee HS, Ryu B, Jiang Y, et al. (2019) Pyrogallol-phloroglucinol-6,6'-Bieckol from *Ecklonia cava* improved blood circulation in diet-induced obese and diet-induced hypertension mouse models. Mar Drugs 17 pii: E272.
92. Wada K, Nakamura K, Tamai Y, Tsuji M, Sahashi Y, et al. (2011) Seaweed intake and blood pressure levels in healthy pre-school Japanese children. Nutrition 10: 83.
93. Wells ML, Potin P, Craigie JS, Raven JA, Merchant SS, et al. (2017) Algae as nutritional and functional food sources: Revisiting our understanding. J Appl Phycol 29: 949-982.
94. Gammone MA, Riccioni G, Parrinello G, D'Orazio N (2018) Omega-3 polyunsaturated fatty acids: Benefits and endpoints in sport. Nutrients 11 pii: E46.
95. Circuncisão AR, Catarino MD, Cardoso SM, Silva AMS (2018) Minerals from macroalgae origin: Health benefits and risks for consumers. Mar Drugs 16 pii: E400.
96. Martínez-Villaluenga C, Peñas E, Rico D, Martín-Diana AB, Portillo MP, et al. (2018) Potential usefulness of a wakame/carob functional snack for the treatment of several aspects of metabolic syndrome: from *in vitro* to *in vivo* studies. Mar Drugs 16 pii: E512.
97. Jung IH, Kim SE, Lee YG, Kim DH, Kim H, et al. (2018) Antihypertensive effect of ethanolic extract from *Acanthopanax sessiliflorus* fruits and quality control of active compounds. Oxid Med Cell Longev 2018: 5158243.
98. Kawamura A, Kajiya K, Kishi H, Inagaki J, Mitarai M, et al. (2018) The nutritional characteristics of the hypotensive WASHOKU-modified DASH diet: A sub-analysis of the DASH-JUMP study. Curr Hypertens Rev 14: 56-65.
99. Fitzgerald C, Aluko RE, Hossain M, Rai DK, Hayes M (2014) Potential of a renin inhibitory peptide from the red seaweed *Palmaria palmata* as a functional food ingredient following confirmation and characterization of a hypotensive effect in spontaneously hypertensive rats. J Agric Food Chem 62: 8352-8356.
100. Cardoso SM, Pereira OR, Seca AM, Pinto DC, Silva AM (2015) Seaweeds as preventive agents for cardiovascular diseases: From nutrients to functional foods. Mar Drugs 13: 6838-6865.
101. Bleakley S, Hayes M (2017) Algal proteins: Extraction, application and challenges concerning production. Foods 6: E33.
102. Sellimi S, Ksouda G, Benslima A, Nasri R, Rinaudo M, et al. (2017) Enhancing color and oxidative stabilities of reduced-nitrite Turkey meat sausages during refrigerated storage using fucoxanthin purified from the Tunisian seaweed *Cystoseira barbata*. Food Chem Toxicol 107: 620-629.
103. Heo SJ, Jeon YJ (2009) Evaluation of diphlorethohydroxycarmalol isolated from *Ishige okamurae* for radical scavenging activity and its protective effect against H₂O₂-induced cell damage. Process Biochem 44: 412-418.
104. Heo SJ, Jeon YJ (2008) Radical scavenging capacity and cytoprotective effect of enzymatic digests of *Ishige okamurae*. J Appl Phycol 20: 1087-1095.
105. Kang MC, Lee SH, Lee WW, Kang N, Kim EA, et al. (2014) Protective effect of fucoxanthin isolated from *Ishige okamurae* against high-glucose induced oxidative stress in human umbilical vein endothelial cells and zebrafish model. J Funct Foods 11: 304-312.
106. Ahn SM, Hong YK, Kwon GS, Sohn HY (2011) Evaluation of antioxidant and nitrite scavenging activity of seaweed extracts. J Life Sci 21: 576-583.
107. Kang MC, Wijesinghe WA, Lee SH, Kang SM, Ko SC, et al. (2013) Dieckol isolated from brown seaweed *Ecklonia cava* attenuates type II diabetes in db/db mouse model. Food Chem Toxicol 53: 294-298.

108. Lee SH, Park MH, Kang SM, Ko SC, Kang MC, et al. (2012) Dieckol isolated from *Ecklonia cava* protects against high-glucose induced damage to rat insulinoma cells by reducing oxidative stress and apoptosis. *Biosci Biotechnol Biochem* 76: 1445-1451.
109. Apostolidis E, Lee CM (2010) *In vitro* potential of *Ascophyllum nodosum* phenolic antioxidant-mediated alpha-glucosidase and alpha-amylase inhibition. *J Food Sci* 75: 97-102.
110. Maeda H (2015) Nutraceutical effects of fucoxanthin for obesity and diabetes therapy: A review. *J Oleo Sci* 64: 125-132.
111. Manandhar B, Paudel P, Seong SH, Jung HA, Choi JS (2019) Characterizing Eckol as a therapeutic aid: A systematic review. *Mar Drugs* 17: 361.
112. Kumar MS (2019) Peptides and peptidomimetics as potential anti-obesity agents: Overview of current status. *Front Nutr* 6: 11.
113. Sanjeeva KKA, Lee WW, Jeon YJ (2018) Nutrients and bioactive potentials of edible green and red seaweed in Korea. *Fish Aquat Sci* 21: 19.
114. Savini I, Catani MV, Evangelista D, Gasperi V, Avigliano L (2013) Obesity-associated oxidative stress: Strategies finalized to improve redox state. *Int J Mol Sci* 14: 10497-10538.
115. Gammone MA, D'Orazio N (2015) Anti-obesity activity of the marine carotenoid fucoxanthin. *Mar Drugs* 13: 2196-2214.
116. Maeda H, Kanno S, Kodate M, Hosokawa M, Miyashita K (2015) Fucoxanthinol, metabolite of fucoxanthin, improves obesity-induced inflammation in adipocyte cells. *Mar Drugs* 13: 4799-813.
117. Catarino MD, Silva AMS, Cardoso SM (2018) Phytochemical constituents and biological activities of *Fucus* spp. *Mar Drugs* 16: 249.
118. Gammone MA, Riccioni G, D'Orazio N (2015) Marine carotenoids against oxidative stress: Effects on human health. *Mar Drugs* 13: 6226-6246.
119. Mhadhebi L, Mhadhebi A, Robert J, Bouraoui A (2014) Antioxidant, anti-inflammatory and antiproliferative effects of aqueous extracts of three Mediterranean brown seaweeds of the genus *Cystoseira*. *Iran J Pharm Res* 13: 207-220.
120. Kiokias S, Proestos C, Oreopoulou V (2018) Effect of natural food antioxidants against LDL and DNA oxidative changes. *Antioxidants (Basel)* 7: 133.
121. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics 2019. *CA Cancer J Clin* 69: 7-34.
122. Shah SC, Kayamba V, Peek RM Jr, Heimbürger D (2019) Cancer control in low- and middle-income countries: Is it time to consider screening? *J Glob Oncol* 5: 1-8.
123. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, et al. (2019) Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 144: 1941-1953.
124. Feng RM, Zong YN, Cao SM, Xu RH (2019) Current cancer situation in China: Good or bad news from the 2018 Global Cancer Statistics? *Cancer Commun (Lond)* 39: 22.
125. WHO (2018) Latest global cancer data: Cancer burden rises to 18. 1 million new cases and 9. 6 million cancer deaths in 2018. Press Release, Accessed on: 12 September, 2018. Available from: <https://www.who.int/cancer/PRGlobocanFinal.pdf>
126. Schüz J, Espina C, Wild CP (2019) Primary prevention: A need for concerted action. *Mol Oncol* 13: 567-578.
127. WHO (2018) Cancer. Health Topics, Accessed on: 12 September, 2018. Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer>
128. AK Mohiuddin (2019) Non-drug pain management: Opportunities to explore (e-book) Publisher: BiomedGrid LLC, USA ISBN: 978-1-946628-01-5.
129. WHO (2018) \$46 billion in productivity lost to cancer in major emerging economies. Press Release, Accessed on: 31 January, 2018. Available from: https://www.iarc.fr/wp-content/uploads/2018/07/pr255_E.pdf
130. <https://www.worldcancerday.org/financial-and-economic-impact>
131. Olivares-Banuelos T, Gutierrez-Rodriguez AG, Mendez-Bellido R, Tovar-Miranda R, Arroyo-Helguera O, et al. (2019) Brown seaweed *Egregia menziesii*'s cytotoxic activity against brain cancer cell lines. *Molecules* 24: 260.
132. Rocha DHA, Seca AML, Pinto DCGA (2018) Seaweed secondary metabolites *in vitro* and *in vivo* anticancer activity. *Mar Drugs* 16: 410.
133. Cho M, Park GM, Kim SN, Amna T, Lee S, et al. (2014) Glioblastoma-specific anticancer activity of pheophorbide a from the edible red seaweed *Grateloupia elliptica*. *J Microbiol Biotechnol* 24: 346-353.
134. Park MN, Song HS, Kim M, Lee MJ, Cho W, et al. (2017) Review of natural product-derived compounds as potent anti-glioblastoma drugs. *Biomed Res Int* 2017: 8139848.

135. Florczyk SJ, Kievit FM, Wang K, Erickson AE, Ellenbogen RG, et al. (2016) 3D porous chitosan-alginate scaffolds promote proliferation and enrichment of cancer stem-like cells. *J Mater Chem B* 4: 6326-6334.
136. Kievit FM, Wang K, Erickson AE, Lan Levengood SK, Ellenbogen RG, et al. (2016) Modeling the tumor microenvironment using chitosan-alginate scaffolds to control the stem-like state of glioblastoma cells. *Biomater Sci* 4: 610-613.
137. Wang K, Kievit FM, Erickson AE, Silber JR, Ellenbogen RG, et al. (2016) Culture on 3D chitosan-hyaluronic acid scaffolds enhances stem cell marker expression and drug resistance in human glioblastoma cancer stem cells. *Adv Healthc Mater* 5: 3173-3181.
138. Xiao W, Sohrabi A, Seidlits SK (2017) Integrating the glioblastoma microenvironment into engineered experimental models. *Future Sci OA* 3: 189.
139. Florczyk SJ, Wang K, Jana S, Wood DL, Sytsma SK, et al. (2013) Porous chitosan-hyaluronic acid scaffolds as a mimic of glioblastoma microenvironment ECM. *Biomaterials* 34: 10143-10150.
140. Palama IE, D'Amone S, Cortese B (2018) Microenvironmental rigidity of 3D Scaffolds and influence on glioblastoma cells: A biomaterial design perspective. *Front Bioeng Biotechnol* 6: 131.
141. Wang K, Kievit FM, Florczyk SJ, Stephen ZR, Zhang M (2015) 3D porous chitosan-alginate scaffolds as an *in vitro* model for evaluating nanoparticle-mediated tumor targeting and gene delivery to prostate cancer. *Biomacromolecules* 16: 3362-3372.
142. Musah-Eroje A, Watson S (2019) A novel 3D *in vitro* model of glioblastoma reveals resistance to temozolomide which was potentiated by hypoxia. *J Neurooncol* 142:231-240.
143. Yang J, Li Y, Zhang T, Zhang X (2016) Development of bioactive materials for glioblastoma therapy. *Bioact Mater* 1: 29-38.
144. Wu HL, Fu XY, Cao WQ, Xiang WZ, Hou YJ, et al. (2019) Induction of apoptosis in human glioma cells by fucoxanthin via triggering of ROS-mediated oxidative damage and regulation of MAPKs and PI3K-AKT pathways. *J Agric Food Chem* 67: 2212-2219.
145. Afzal S, Garg S, Ishida Y, Terao K, Kaul SC, et al. (2019) Rat glioma cell-based functional characterization of anti-stress and protein deaggregation activities in the marine carotenoids, astaxanthin and fucoxanthin. *Mar Drugs* 17: 189.
146. Garg S, Afzal S, Elwakeel A, Sharma D, Radhakrishnan N, et al. (2019) Marine carotenoid fucoxanthin possesses anti-metastasis activity: Molecular evidence. *Mar Drugs* 17: 338.
147. Miao L, Chi S, Wu M, Liu Z, Li Y (2019) Deregulation of phytoene- β -carotene synthase results in depression of astaxanthin synthesis at high glucose concentration in *Phaffia rhodozyma* astaxanthin-overproducing strain MK19. *BMC Microbiol* 19: 133.
148. Liu Y, Zheng J, Zhang Y, Wang Z, Yang Y, et al. (2016) Fucoxanthin activates apoptosis via inhibition of PI3K/Akt/mTOR pathway and suppresses invasion and migration by restriction of p38-MMP-2/9 pathway in human glioblastoma cells. *Neurochem Res* 41: 2728-2751.
149. Zhang L, Wang H, Xu J, Zhu J, Ding K (2014) Inhibition of cathepsin S induces autophagy and apoptosis in human glioblastoma cell lines through ROS-mediated PI3K/AKT/mTOR/p70S6K and JNK signaling pathways. *Toxicol Lett* 228: 248-59.
150. Hormozi M, Ghoreishi S, Baharvand P (2019) Astaxanthin induces apoptosis and increases activity of antioxidant enzymes in LS-180 cells. *Artif Cells Nanomed Biotechnol* 47: 891-895.
151. Lu DY, Chang CS, Yeh WL, Tang CH, Cheung CW, et al. (2012) The novel phloroglucinol derivative BFP induces apoptosis of glioma cancer through reactive oxygen species and endoplasmic reticulum stress pathways. *Phytomedicine* 19: 1093-1100.
152. Pinhatti AV, de Barros FM, de Farias CB, Schwartzmann G, Poser GL, et al. (2013) Antiproliferative activity of the dimeric phloroglucinol and benzophenone derivatives of *Hypericum* spp. native to southern Brazil. *Anticancer Drugs* 24: 699-703.
153. Jakobs D, Hage-Hülsmann A, Prenner L, Kolb C, Weiser D, et al. (2013) Downregulation of $\beta 1$ -adrenergic receptors in rat C6 glioblastoma cells by hyperforin and hyperoside from St John's wort. *J Pharm Pharmacol* 65: 907-915.
154. Lai SW, Huang BR, Liu YS, Lin HY, Chen CC, et al. (2018) Differential characterization of temozolomide-resistant human glioma cells. *Int J Mol Sci* 19: 127.
155. Tsai CF, Yeh WL, Chen JH, Lin C, Huang SS, et al. (2014) Osthole suppresses the migratory ability of human glioblastoma multiform cells via inhibition of focal adhesion kinase-mediated matrix metalloproteinase-13 expression. *Int J Mol Sci* 15: 3889-3903.
156. Alghazwi M, Smid S, Musgrave I, Zhang W (2019) *In vitro* studies of the neuroprotective activities of astaxanthin and fucoxanthin against amyloid beta (A β (1-42)) toxicity and aggregation. *Neurochem Int* 124: 215-224.

157. Raposo MF, de Morais AM, de Morais RM (2015) Carotenoids from marine microalgae: A valuable natural source for the prevention of chronic diseases. *Mar Drugs* 13: 5128-5155.
158. Peng J, Yuan JP, Wu CF, Wang JH (2011) Fucoxanthin, a marine carotenoid present in brown seaweeds and diatoms: Metabolism and bioactivities relevant to human health. *Mar Drugs* 9: 1806-1828.
159. Hsu HY, Hwang PA (2019) Clinical applications of fucoidan in translational medicine for adjuvant cancer therapy. *Clin Transl Med* 8: 15.
160. van Weelden G, Bobinski M, Okla K, van Weelden WJ, Romano A, et al. (2019) Fucoidan structure and activity in relation to anti-cancer mechanisms. *Mar Drugs* 17: 32.
161. Wang Y, Xing M, Cao Q, Ji A, Liang H, et al. (2019) Biological activities of fucoidan and the factors mediating its therapeutic effects: A review of recent studies. *Mar Drugs* 17: 183.
162. Misra P, Singh S (2019) Role of cytokines in combinatorial immunotherapeutics of non-small cell lung cancer through systems perspective. *Cancer Med* 8: 1976-1995.
163. Ercolano G, De Cicco P, Ianaro A (2019) New drugs from the sea: Pro-apoptotic activity of sponges and algae derived compounds. *Mar Drugs* 17: 31.
164. Erfani N, Nazemosadat Z, Moein M (2015) Cytotoxic activity of ten algae from the Persian Gulf and Oman Sea on human breast cancer cell lines; MDA-MB-231, MCF-7, and T-47D. *Pharmacognosy Res* 7: 133-137.
165. Wu SY, Wu AT, Yuan KS, Liu SH (2016) Brown seaweed fucoidan inhibits cancer progression by dual regulation of mir-29c/ADAM12 and miR-17-5p/PTEN axes in human breast cancer cells. *J Cancer* 7: 2408-2419.
166. Moussavou G, Kwak DH, Obiang-Obonou BW, Maranguy CA, Dinzouna-Boutamba SD, et al. (2014) Anticancer effects of different seaweeds on human colon and breast cancers. *Mar Drugs* 12: 4898-4911.
167. Montuori N, Pesapane A, Rossi FW, Giudice V, De Paulis A, et al. (2016) Urokinase type plasminogen activator receptor (uPAR) as a new therapeutic target in cancer. *Transl Med UniSa* 15: 15-21.
168. Teas J, Vena S, Cone DL, Irhimeh M (2013) The consumption of seaweed as a protective factor in the etiology of breast cancer: Proof of principle. *J Appl Phycol* 25: 771-779.
169. Shamsabadi FT, Khoddami A, Fard SG, Abdullah R, Othman HH, et al. (2013) Comparison of tamoxifen with edible seaweed (*Eucheuma cottonii* L.) extract in suppressing breast tumor. *Nutr Cancer* 65: 255-262.
170. Jazara M, Ghannam A, Soukkaieh C, Murad H (2016) Anti-proliferative activity of λ -carrageenan through the induction of apoptosis in human breast cancer cells. *Int J Cancer Manag* 9: e3836.
171. Groult H, Cousin R, Chot-Plassot C, Maura M, Bridiau N, et al. (2019) λ -carrageenan oligosaccharides of distinct anti-heparanase and anticoagulant activities inhibit MDA-MB-231 breast cancer cell migration. *Mar Drugs* 17: 140.
172. Losada-Echeberria M, Herranz-Lopez M, Micol V, Barragon-Catalan E (2017) Polyphenols as promising drugs against main breast cancer signatures. *Antioxidants (Basel)* 6: 88.
173. Namvar F, Mohamad R, Baharara J, Zafar-Balanejad S, Fargahi F, et al. (2013) Antioxidant, anti-proliferative, and anti-angiogenesis effects of polyphenol-rich seaweed (*Sargassum muticum*). *Biomed Res Int* 2013: 604787.
174. Niedzwiecki A, Roomi MW, Kalinovsky T, Rath M (2016) Anticancer efficacy of polyphenols and their combinations. *Nutrients* 8: 552.
175. Kapinova A, Kubatka P, Golubnitschaja O, Kello M, Zubor P, et al. (2018) Dietary phytochemicals in breast cancer research: Anticancer effects and potential utility for effective chemoprevention. *Environ Health Prev Med* 23: 36.
176. Keating E, Martel F (2018) Anti-metabolic effects of polyphenols in breast cancer cells: Focus on glucose uptake and metabolism. *Front Nutr* 5: 25.
177. Sudhakaran M, Sardesai S, Doseff AI (2019) Flavonoids: New frontier for immuno-regulation and breast cancer control. *Antioxidants (Basel)* 8: 103.
178. Hui C, Qi X, Qianrong Z, Xiaoli P, Jundong Z, et al. (2013) Flavonoids, flavonoid subclasses and breast cancer risk: A meta-analysis of epidemiologic studies. *PLoS One* 8: e54318.
179. Sak K (2017) Epidemiological evidences on dietary flavonoids and breast cancer risk: A narrative review. *Asian Pac J Cancer Prev* 18: 2309-2328.
180. Takemura H, Sakakibara H, Yamazaki S, Shimoi K (2013) Breast cancer and flavonoids - A role in prevention. *Curr Pharm Des* 19: 6125-6132.
181. Batra P, Sharma AK (2013) Anti-cancer potential of flavonoids: Recent trends and future perspectives. *Biotech* 3: 439-459.
182. Magne Nde CB, Zingue S, Winter E, Creczynski-Pasa TB, Michel T, et al. (2015) Flavonoids, breast cancer

- chemopreventive and/or chemotherapeutic agents. *Curr Med Chem* 22: 3434-3446.
183. Abotaleb M, Samuel SM, Varghese E, Varghese S, Kubatka P, et al. (2018) Flavonoids in cancer and apoptosis. *Cancers (Basel)* 11: 28.
 184. Pang BB, Chu YK, Yang H (2018) Anti-breast cancer mechanism of flavonoids. *Zhongguo Zhong Yao Za Zhi* 43: 913-920.
 185. Zhang HW, Hu JJ, Fu RQ, Liu X, Zhang YH, et al. (2018) Flavonoids inhibit cell proliferation and induce apoptosis and autophagy through downregulation of PI3K γ mediated PI3K/AKT/mTOR/p70S6K/ULK signaling pathway in human breast cancer cells. *Sci Rep* 8: 11255.
 186. Rodriguez-Gariía C, Sanchez-Quesada C, J Gaforio J (2019) Dietary flavonoids as cancer chemopreventive agents: An updated review of human studies. *Antioxidants (Basel)* 8: 137.
 187. Atashrazm F, Lowenthal RM, Woods GM, Holloway AF, Dickinson JL (2015) Fucoidan and cancer: A multifunctional molecule with anti-tumor potential. *Mar Drugs* 13: 2327-2346.
 188. Lu J, Shi KK, Chen S, Wang J, Hassouna A, et al. (2018) Fucoidan extracted from the New Zealand *Undaria pinnatifida* - Physicochemical comparison against five other fucoidans: Unique low molecular weight fraction bioactivity in breast cancer cell lines. *Mar Drugs* 16: 461.
 189. Zorofchian Moghadamtousi S, Karimian H, Khanabdali R, Razavi M, Firoozinia M, et al. (2014) Anticancer and antitumor potential of fucoidan and fucoxanthin, two main metabolites isolated from brown algae. *Scientific World Journal* 2014: 768323.
 190. Xue M, Ge Y, Zhang J, Wang Q, Hou L, et al. (2012) Anti-cancer properties and mechanisms of fucoidan on mouse breast cancer *in vitro* and *in vivo*. *PLoS One* 7: e43483.
 191. Pawar VK, Singh Y, Sharma K, Shrivastav A, Sharma A, et al. (2019) Improved chemotherapy against breast cancer through immunotherapeutic activity of fucoidan decorated electrostatically assembled nanoparticles bearing doxorubicin. *Int J Biol Macromol* 122: 1100-1114.
 192. He X, Xue M, Jiang S, Li W, Yu J, et al. (2019) Fucoidan promotes apoptosis and inhibits EMT of breast cancer cells. *Biol Pharm Bull* 42: 442-447.
 193. Xue M, Ge Y, Zhang J, Liu Y, Wang Q, et al. (2013) Fucoidan inhibited 4T1 mouse breast cancer cell growth *in vivo* and *in vitro* via downregulation of Wnt/ β -catenin signaling. *Nutr Cancer* 65: 460-468.
 194. Xue M, Ji X, Liang H, Liu Y, Wang B, et al. (2018) The effect of fucoidan on intestinal flora and intestinal barrier function in rats with breast cancer. *Food Funct* 9: 1214-1223.
 195. Oliveira C, Neves NM, Reis RL, Martins A, Silva TH (2018) Gemcitabine delivered by fucoidan/chitosan nanoparticles presents increased toxicity over human breast cancer cells. *Nanomedicine (Lond)* 13: 2037-2050.
 196. Gong X, Smith JR, Swanson HM, Rubin LP (2018) Carotenoid lutein selectively inhibits breast cancer cell growth and potentiates the effect of chemotherapeutic agents through ROS-mediated mechanisms. *Molecules* 23: 905.
 197. Chang J, Zhang Y, Li Y, Lu K, Shen Y, et al. (2018) NrF2/ARE and NF- κ B pathway regulation may be the mechanism for lutein inhibition of human breast cancer cell. *Future Oncol* 14: 719-726.
 198. Mignone LI, Giovannucci E, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, et al. (2009) Dietary carotenoids and the risk of invasive breast cancer. *Int J Cancer* 124: 2929-2937.
 199. Li Y, Zhang Y, Liu X, Wang M, Wang P, et al. (2018) Lutein inhibits proliferation, invasion and migration of hypoxic breast cancer cells via downregulation of HES1. *Int J Oncol* 52: 2119-2129.
 200. Yan B, Lu MS, Wang L, Mo XF, Luo WP, et al. (2016) Specific serum carotenoids are inversely associated with breast cancer risk among Chinese women: A case-control study. *Br J Nutr* 115: 129-137.
 201. Li YX, Himaya SW, Dewapriya P, Zhang C, Kim SK (2013) Fumigaclavine C from a marine-derived fungus *Aspergillus fumigatus* induces apoptosis in MCF-7 breast cancer cells. *Mar Drugs* 11: 5063-5086.
 202. Dyshlovoy SA, Honecker F (2015) Marine compounds and cancer: Where do we stand? *Mar Drugs* pp: 5657-5665.
 203. Vaikundamoorthy R, Krishnamoorthy V, Vilwanathan R, Rajendran R (2018) Structural characterization and anticancer activity (MCF7 and MDA-MB-231) of polysaccharides fractionated from brown seaweed *Sargassum wightii*. *Int J Biol Macromol* 111: 1229-1237.
 204. Sithranga Boopathy N, Kathiresan K. (2010) Anticancer drugs from marine flora: An overview. *J Oncol* 2010: 1-18.
 205. Abd-Ellatef GF, Ahmed OM, Abdel-Reheim ES, Abdel-Hamid AZ (2017) *Ulva lactuca* polysaccharides prevent Wistar rat breast carcinogenesis through the augmentation of apoptosis, enhancement of antioxidant

- defense system, and suppression of inflammation. Breast Cancer (Dove Med Press) 9: 67-83.
206. Fedorov SN, Ermakova SP, Zvyagintseva TN, Stonik VA (2013) Anticancer and cancer preventive properties of marine polysaccharides: Some results and prospects. Mar Drugs 11: 4876-4901.
 207. Ghannam A, Murad H, Jazzara M, Odeh A, Allaf AW (2018) Isolation, structural characterization and anti-proliferative activity of phycocolloids from the red seaweed *Laurencia papillosa* on MCF-7 human breast cancer cells. Int J Biol Macromol 108: 916-926.
 208. Vishchuk OS, Ermakova SP, Zvyagintseva TN (2011) Sulfated polysaccharides from brown seaweeds *Saccharina japonica* and *Undaria pinnatifida*: Isolation, structural characteristics and antitumor activity. Carbohydr Res 346: 2769-2776.
 209. Vaseghi G, Sharifi M, Dana N, Ghasemi A, Yegdaneh A (2018) Cytotoxicity of *Sargassum angustifolium* partitions against breast and cervical cancer cell lines. Adv Biomed Res 7: 43.
 210. Kim EK, Tang Y, Kim YS, Hwang JW, Choi EJ, et al. (2015) First evidence that *Ecklonia cava*-derived dieckol attenuates MCF-7 human breast carcinoma cell migration. Mar Drugs 13: 1785-1797.
 211. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, et al. (2019) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol pp: 1-42.
 212. Recio-Boiles A, Waheed A, Cagir B (2019) Cancer, colon. [Updated 2019 Jun 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Available from: <https://www.ncbi.nlm.nih.gov/books/NBK470380/>
 213. Thanikachalam K, Khan G (2019) Colorectal cancer and nutrition. Nutrients 11: 164.
 214. Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, et al. (2017) Foods and beverages and colorectal cancer risk: A systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol 28: 1788-1802.
 215. Kim J, Lee J, Oh JH, Chang HJ, Sohn DK, et al. (2019) Associations among dietary seaweed intake, c-MYC rs6983267 polymorphism and risk of colorectal cancer in a Korean population: A case-control study. Eur J Nutr pp: 1-12.
 216. Zhao Y, Zheng Y, Wang J, Ma S, Yu Y, et al. (2018) Fucoxanthin extracted from *Undaria pinnatifida*: Source for nutraceuticals/functional foods. Mar Drugs 16: E321.
 217. Tsai HL, Tai CJ, Huang CW, Chang FR, Wang JY (2017) Efficacy of low-molecular-weight fucoidan as a supplemental therapy in metastatic colorectal cancer patients: A double-blind randomized controlled trial. Mar Drugs 15 pii: E122.
 218. Wang SK, Li Y, White WL, Lu J (2014) Extracts from New Zealand *Undaria pinnatifida* containing fucoxanthin as potential functional biomaterials against cancer *in vitro*. J Funct Biomater 5: 29-42.
 219. Han YS, Lee JH, Lee SH (2015) Fucoidan inhibits the migration and proliferation of HT-29 human colon cancer cells via the phosphoinositide-3 kinase/Akt/mechanistic target of rapamycin pathways. Mol Med Rep 12: 3446-3452.
 220. Han YS, Lee JH, Lee SH (2015) Anti-tumor effects of fucoidan on human colon cancer cells via activation of Akt signaling. Biomol Ther (Seoul) 23: 225-232.
 221. Chen LM, Liu PY, Chen YA, Tseng HY, Shen PC, et al. (2017) Oligo-fucoidan prevents IL-6 and CCL2 production and cooperates with p53 to suppress ATM signaling and tumor progression. Sci Rep 7: 11864.
 222. Kim SK, Karagozlu MZ (2011) Marine algae: Natural product source for the gastrointestinal Cancer Treatment. In: Marine Medicinal Foods: Implications and Applications, Macro and Microalgae. ISSN 1043-4526. Editors: Se-Kwon Kim, Steve Taylor Publisher: Academic Press, 2011 ISBN 0123876699, 9780123876690. Adv Food Nutr Res 64.
 223. Bakunina I, Chadova O, Malyarenko O, Ermakova S (2018) The effect of fucoidan from the brown alga *Fucus evanescence* on the activity of α -N-acetylgalactosaminidase of human colon carcinoma cells. Mar Drugs 16: pii: E155.
 224. Kim IH, Kwon MJ, Nam TJ (2017) Differences in cell death and cell cycle following fucoidan treatment in high-density HT-29 colon cancer cells. Mol Med Rep 15: 4116-4122.
 225. Kim HY, Kim YM, Hong S (2019) Astaxanthin suppresses the metastasis of colon cancer by inhibiting the MYC-mediated downregulation of microRNA-29a-3p and microRNA-200a. Sci Re 9: 9457.
 226. Nagendraprabhu P, Sudhandiran G (2011) Astaxanthin inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating the expressions of ERK-2, NFkB and COX-2. Invest New Drugs 29: 207-24.
 227. Yasui Y, Hosokawa M, Mikami N, Miyashita K, Tanaka T (2011) Dietary astaxanthin inhibits colitis and colitis-associated colon carcinogenesis in mice via

- modulation of the inflammatory cytokines. *Chem Biol Interact* 193: 79-87.
228. Liu X, Song M, Gao Z, Cai X, Dixon W, et al. (2016) Stereoisomers of astaxanthin inhibit human colon cancer cell growth by inducing G2/M cell cycle arrest and apoptosis. *J Agric Food Chem* 64: 7750-7759.
 229. Wayakanon K, Rueangyotchanthana K, Wayakanon P, Suwannachart C (2018) The inhibition of Caco-2 proliferation by astaxanthin from *Xanthophyllomyces dendrorhous*. *J Med Microbiol* 67: 507-513.
 230. Tanaka T, Kawamori T, Ohnishi M, Makita H, Mori H, et al. (1995) Suppression of azoxymethane-induced rat colon carcinogenesis by dietary administration of naturally occurring xanthophylls astaxanthin and canthaxanthin during the postinitiation phase. *Carcinogenesis* 16: 2957-63.
 231. Terasaki M, Iida T, Kikuchi F, Tamura K, Endo T, et al. (2019) Fucoxanthin potentiates anoikis in colon mucosa and prevents carcinogenesis in AOM/DSS model mice. *J Nutr Biochem* 64: 198-205.
 232. Terasaki M, Masaka S, Fukada C, Houzaki M, Endo T, et al. (2019) Salivary glycine is a significant predictor for the attenuation of polyp and tumor microenvironment formation by fucoxanthin in AOM/DSS mice. *In Vivo* 33: 365-374.
 233. Terasaki M, Matsumoto N, Hashimoto R, Endo T, Maeda H, et al. (2019) Fucoxanthin administration delays occurrence of tumors in xenograft mice by colonospheres, with an anti-tumor predictor of glycine. *J Clin Biochem Nutr* 64: 52-58.
 234. Das SK, Hashimoto T, Shimizu K, Yoshida T, Sakai T, et al. (2005) Fucoxanthin induces cell cycle arrest at G0/G1 phase in human colon carcinoma cells through up-regulation of p21WAF1/Cip1. *Biochim Biophys Acta* 1726: 328-335.
 235. Hosokawa M, Kudo M, Maeda H, Kohno H, Tanaka T, et al. (2004) Fucoxanthin induces apoptosis and enhances the anti-proliferative effect of the PPARgamma ligand, troglitazone, on colon cancer cells. *Biochim Biophys Acta* 1675: 113-119.
 236. Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, et al. (1998) Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation. *Carcinogenesis* 19: 81-85.
 237. Konishi I, Hosokawa M, Sashima T, Kobayashi H, Miyashita K (2006) Halocynthiaxanthin and fucoxanthinol isolated from *Halocynthia roretzi* induce apoptosis in human leukemia, breast and colon cancer cells. *Comp Biochem Physiol C Toxicol Pharmacol* 142: 53-59.
 238. Kim J, Lee J, Oh JH, Chang HJ, Sohn DK, et al. (2019) Dietary lutein plus zeaxanthin intake and DICER1 rs3742330 A>G polymorphism relative to colorectal cancer risk. *Sci Rep* 9: 3406.
 239. Reynoso-Camacho R, González-Jasso E, Ferriz-Martínez R, Villalón-Corona B, Loarca-Piña GF, et al. (2011) Dietary supplementation of lutein reduces colon carcinogenesis in DMH-treated rats by modulating K-ras, PKB and β -catenin proteins. *Nutr Cancer* 63: 39-45.
 240. Grudzinski W, Piet M, Luchowski R, Reszczynska E, Welc R, et al. (2018) Different molecular organization of two carotenoids, lutein and zeaxanthin, in human colon epithelial cells and colon adenocarcinoma cells. *Spectrochim Acta A Mol Biomol Spectrosc* 188: 57-63.
 241. Kohler LN, Harris RB, Oren E, Roe DJ, Lance P, et al. (2018) Adherence to nutrition and physical activity cancer prevention guidelines and development of colorectal adenoma. *Nutrients* 10 pii: E1098.
 242. Wang ZJ, Ohnaka K, Morita M, Toyomura K, Kono S, et al. (2013) Dietary polyphenols and colorectal cancer risk: The Fukuoka colorectal cancer study. *World J Gastroenterol* 19: 2683-2690.
 243. Alam MN, Almoyad M, Huq F (2018) Polyphenols in colorectal cancer: current state of knowledge including clinical trials and molecular mechanism of action. *Biomed Res Int* 2018: 4154185.
 244. Murphy N, Achaintre D, Zamora-Ros R, Jenab M, Boutron-Ruault MC, et al. (2018) A prospective evaluation of plasma polyphenol levels and colon cancer risk. *Int J Cancer* 143: 1620-1631.
 245. Mileo AM, Nisticò P, Miccadei S (2019) Polyphenols: Immunomodulatory and therapeutic implication in colorectal cancer. *Front Immunol* 10: 729.
 246. Zamora-Ros R, Cayssials V, Jenab M, Rothwell JA, Fedirko V, et al. (2018) Dietary intake of total polyphenol and polyphenol classes and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Eur J Epidemiol* 33: 1063-1075.
 247. Van der Veen DJ, Döpp CME, Siemonsma PC, Nijhuis-van der Sanden MWG, de Swart BJM, et al. (2019) Factors influencing the implementation of home-based stroke rehabilitation: Professionals' perspective. *PLoS One* 14: e0220226.
 248. Galasso C, Orefice I, Pellone P, Cirino P, Miele R, et al. (2018) On the neuroprotective role of astaxanthin: New perspectives? *Mar Drugs* 16 pii: E247.
 249. Deng X, Wang M, Hu S, Feng Y, Shao Y, et al. (2019) The neuroprotective effect of astaxanthin on

- pilocarpine-induced status epilepticus in rats. *Front Cell Neurosci* 13: 123.
250. Grimmig B, Kim SH, Nash K, Bickford PC, Douglas Shytle R (2017) Neuroprotective mechanisms of astaxanthin: A potential therapeutic role in preserving cognitive function in age and neurodegeneration. *Geroscience* 39: 19-32.
 251. Alghazwi M, Smid S, Zhang W. In vitro protective activity of South Australian marine sponge and macroalgae extracts against amyloid beta (A β (1-42)) induced neurotoxicity in PC-12 cells. *Neurotoxicol Teratol* 68: 72-83.
 252. Cho KS, Shin M, Kim S, Lee SB (2018) Recent advances in studies on the therapeutic potential of dietary carotenoids in neurodegenerative diseases. *Oxid Med Cell Longev* 2018: 4120458.
 253. Grimmig B, Daly L, Subbarayan M, Hudson C, Williamson R, et al. (2017) Astaxanthin is neuroprotective in an aged mouse model of Parkinson's disease. *Oncotarget* 9: 10388-10401.
 254. Sathasivam R, Ki JS (2018) A review of the biological activities of microalgal carotenoids and their potential use in healthcare and cosmetic industries. *Mar Drugs* 16 pii: E26.
 255. Bahonar A, Saadatnia M, Khorvash F, Maracy M, Khosravi A (2017) Carotenoids as potential antioxidant agents in stroke prevention: A systematic review. *Int J Prev Med* 8: 70.
 256. Olasehinde TA, Olaniran AO, Okoh AI (2017) Therapeutic Potentials of Microalgae in the Treatment of Alzheimer's Disease. *Molecules* 22 pii: E480.
 257. Wu H, Niu H, Shao A, Wu C, Dixon BJ, et al. (2015) Astaxanthin as a Potential Neuroprotective Agent For Neurological Diseases. *Mar Drugs* 13: 5750-5766.
 258. Barros MP, Poppe SC, Bondan EF (2014) Neuroprotective properties of the marine carotenoid astaxanthin and omega-3 fatty acids and perspectives for the natural combination of both in krill oil. *Nutrients* 6: 1293-317.
 259. Wen X, Huang A, Hu J, Zhong Z, Liu Y, et al. (2015) Neuroprotective effect of astaxanthin against glutamate-induced cytotoxicity in HT22 cells: Involvement of the Akt/GSK-3 β pathway. *Neuroscience* 303: 558-568.
 260. Ito N, Saito H, Seki S, Ueda F, Asada T (2018) Effects of composite supplement containing astaxanthin and sesamin on cognitive functions in people with mild cognitive impairment: A randomized, double-blind, placebo-controlled trial. *J Alzheimers Dis* 62: 1767-1775.
 261. Yamagishi R, Aihara M (2014) Neuroprotective effect of astaxanthin against rat retinal ganglion cell death under various stresses that induce apoptosis and necrosis. *Mol Vis* 20: 1796-805.
 262. Zhang XS, Zhang X, Wu Q, Li W, Wang CX, et al. (2014) Astaxanthin offers neuroprotection and reduces neuroinflammation in experimental subarachnoid hemorrhage. *J Surg Res* 192: 206-213.
 263. Zhang XS, Zhang X, Zhou ML, Zhou XM, Li N, et al. (2014) Amelioration of oxidative stress and protection against early brain injury by astaxanthin after experimental subarachnoid hemorrhage. *J Neurosurg* 121: 42-54.
 264. Yu J, Lin JJ, Yu R, He S, Wang QW, et al. (2017) Fucoxanthin prevents H₂O₂-induced neuronal apoptosis via concurrently activating the PI3-K/Akt cascade and inhibiting the ERK pathway. *Food Nutr Res* 61: 1304678.
 265. Zhang L, Wang H, Fan Y, Gao Y, Li X, et al. (2017) Fucoxanthin provides neuroprotection in models of traumatic brain injury via the Nrf2-ARE and Nrf2-autophagy pathways. *Sci Rep* 7: 46763.
 266. Lin J, Yu J, Zhao J, Zhang K, Zheng J, et al. (2017) Fucoxanthin, a marine carotenoid, attenuates β -amyloid oligomer-induced neurotoxicity possibly via regulating the PI3K/Akt and the ERK pathways in SH-SY5Y cells. *Oxid Med Cell Longev* 2017: 6792543.
 267. Barbosa M, Valentão P, Andrade PB (2014) Bioactive compounds from macroalgae in the new millennium: implications for neurodegenerative diseases. *Mar Drugs* 12: 4934-4972.
 268. Giacompo S, Galuppo M, Montaut S, Iori R, Rollin P, et al. (2015) An overview on neuroprotective effects of isothiocyanates for the treatment of neurodegenerative diseases. *Fitoterapia* 106: 12-21.
 269. Barbalace MC, Malaguti M, Giusti L, Lucacchini A, Hrelia S, et al. (2019) Anti-inflammatory activities of marine algae in neurodegenerative diseases. *Int J Mol Sci* 20 pii: E3061.
 270. Lim CS, Jin DQ, Sung JY, Lee JH, Choi HG, et al. (2006) Antioxidant and anti-inflammatory activities of the methanolic extract of *Neorhodomela aculeate* in hippocampal and microglial cells. *Biol Pharm Bull* 29: 1212-1216.
 271. Kang SM, Cha SH, Ko JY, Kang MC, Kim D, et al. (2012) Neuroprotective effects of phlorotannins isolated from a brown alga, *Ecklonia cava*, against H₂O₂-induced oxidative stress in murine hippocampal HT22 cells. *Environ Toxicol Pharmacol* 34: 96-105.

272. Kim JH, Lee NS, Jeong YG, Lee JH, Kim EJ, et al. (2012) Protective efficacy of an *Ecklonia cava* extract used to treat transient focal ischemia of the rat brain. *Anat Cell Biol* 45: 103-113.
273. Lee S, Youn K, Kim DH, Ahn MR, Yoon E, et al. (2018) Anti-neuroinflammatory property of phlorotannins from *Ecklonia cava* on A β (25-35)-induced damage in PC12 cells. *Mar Drugs* 17 pii: E7.
274. Park SK, Kang JY, Kim JM, Park SH, Kwon BS, et al. (2018) Protective effect of fucoidan extract from *Ecklonia cava* on hydrogen peroxide-induced neurotoxicity. *J Microbiol Biotechnol* 28: 40-49.
275. Cui Y, Amarsanaa K, Lee JH, Rhim JK, Kwon JM, et al. (2019) Neuroprotective mechanisms of dieckol against glutamate toxicity through reactive oxygen species scavenging and nuclear factor-like 2/heme oxygenase-1 pathway. *Korean J Physiol Pharmacol* 23: 121-130.
276. Reid SNS, Ryu JK, Kim Y, Jeon BH (2018) The Effects of fermented *Laminaria japonica* on short-term working memory and physical fitness in the elderly. *Evid Based Complement Alternat Med*: 8109621.
277. Reid SNS, Ryu JK, Kim Y, Jeon BH (2018) GABA-enriched fermented *Laminaria japonica* improves cognitive impairment and neuroplasticity in scopolamine- and ethanol-induced dementia model mice. *Nutr Res Pract* 12: 199-207.
278. Wang J, Zhang Q, Zhang Z, Li Z (2008) Antioxidant activity of sulfated polysaccharide fractions extracted from *Laminaria japonica*. *Int J Biol Macromol* 42: 127-32.
279. Wang J, Liu H, Jin W, Zhang H, Zhang Q (2016) Structure-activity relationship of sulfated hetero/galactofucan polysaccharides on dopaminergic neuron. *Int J Biol Macromol* 82: 878-83.
280. Wang J, Liu H, Zhang X, Li X, Geng L, et al. (2017) Sulfated hetero-polysaccharides protect SH-SY5Y Cells from H₂O₂-induced apoptosis by affecting the PI3K/Akt signaling pathway. *Mar Drugs* 15 pii: E110.
281. Zhang L, Hao J, Zheng Y, Su R, Liao Y, et al. (2018) Fucoidan protects dopaminergic neurons by enhancing the mitochondrial function in a rotenone-induced rat model of Parkinson's disease. *Aging Dis* 9: 590-604.
282. Alghazwi M, Smid S, Karpinić S, Zhang W (2019) Comparative study on neuroprotective activities of fucoidans from *Fucus vesiculosus* and *Undaria pinnatifida*. *Int J Biol Macromol* 122: 255-264.
283. Silva J, Alves C, Pinteus S, Mendes S, Pedrosa R (2018) Neuroprotective effects of seaweeds against 6-hydroxydopamine-induced cell death on an *in vitro* human neuroblastoma model. *BMC Complement Altern Med* 18: 58.
284. Jhamandas JH, Wie MB, Harris K, MacTavish D, Kar S (2005) Fucoidan inhibits cellular and neurotoxic effects of beta-amyloid (A β) in rat cholinergic basal forebrain neurons. *Eur J Neurosci* 21: 2649-2659.
285. Kim SK, Pangestuti R (2013) Prospects and potential application of seaweeds as neuroprotective agents. In: Se-Kwon Kim. *Marine Nutraceuticals: Prospects and Perspectives* Publisher: CRC Press, ISBN 1466513527, 9781466513525.
286. Dewapriya P, Kim SK (2015) Marine algae for protecting your brain: Neuroprotective potentials of marine algae. In: Se-Kwon Kim, Katarzyna Chojnacka. *Marine Algae Extracts, 2 Set: Processes, Products, and Applications*. Publisher: John Wiley & Sons ISBN 3527337083, 9783527337088.
287. Burchell SR, Iniahe LO, Zhang JH, Tang J (2015) Fucoidan from *Fucus vesiculosus* fails to improve outcomes following intracerebral hemorrhage in mice. In: Richard L. Applegate, Gang Chen, Hua Feng, John H. Zhang. *Brain Edema XVI: Translate Basic Science into Clinical Practice* 121 of *Acta Neurochirurgica Supplement*, Publisher: Springer ISBN 3319184970, 9783319184975.
288. Yende SR, Harle UN, Chaugule BB. (2014) Therapeutic potential and health benefits of *Sargassum* species. *Pharmacogn Rev* 8: 1-7.
289. Pinteus S, Lemos MFL, Silva J, Alves C, Neugebauer A, et al. (2017) An insight into *Sargassum muticum* cytoprotective mechanisms against oxidative stress on a human cell *in vitro* model. *Mar Drugs* 15 pii: E353.
290. Bogie J, Hoeks C, Schepers M, Tiane A, Cuypers A, et al. (2019) Dietary *Sargassum fusiforme* improves memory and reduces amyloid plaque load in an Alzheimer's disease mouse model. *Sci Rep* 9: 4908.
291. Zhao D, Zheng L, Qi L, Wang S, Guan L, et al. (2016) Structural features and potent antidepressant effects of total sterols and β -sitosterol extracted from *Sargassum horneri*. *Mar Drugs* 14 pii: E123.
292. Jin W, Liu B, Li S, Chen J, Tang H, et al. (2018) The structural features of the sulfated heteropolysaccharide (ST-1) from *Sargassum thunbergii* and its neuroprotective activities. *Int J Biol Macromol* 108: 307-313.
293. Huang CY, Kuo CH, Chen PW (2017) Compressional-puffing pretreatment enhances neuroprotective effects of fucoidans from the brown seaweed *Sargassum hemiphyllum* on 6-hydroxydopamine-induced apoptosis in SH-SY5Y Cells. *Molecules* 23 pii: E78.

294. Jin W, Zhang W, Wang J, Yao J, Xie E, et al. (2014) A study of neuroprotective and antioxidant activities of heteropolysaccharides from six *Sargassum* species. *Int J Biol Macromol* 67: 336-342.
295. Jin W, Zhang W, Wang J, Zhang Q (2013) The neuroprotective activities and antioxidant activities of the polysaccharides from *Saccharina japonica*. *Int J Biol Macromol* 58: 240-244.
296. Torres MD, Flórez-Fernández N, Domínguez H (2019) Integral utilization of red seaweed for bioactive production. *Mar Drugs* 17 pii: E314.
297. Jin DQ, Lim CS, Sung JY, Choi HG, Ha I, et al. (2006) *Ulva conglobata*, a marine alga, has neuroprotective and anti-inflammatory effects in murine hippocampal and microglial cells. *Neurosci Lett* 402: 154-158.
298. Suganthi N, Karutha Pandian S, Pandima Devi K (2010) Neuroprotective effect of seaweeds inhabiting South Indian coastal area (Hare Island, Gulf of Mannar Marine Biosphere Reserve): Cholinesterase inhibitory effect of *Hypnea valentiae* and *Ulva reticulata*. *Neurosci Lett* 468: 216-219.
299. Ratnayake R, Liu Y, Paul VJ, Luesch H (2013) Cultivated sea lettuce is a multiorgan protector from oxidative and inflammatory stress by enhancing the endogenous antioxidant defense system. *Cancer Prev Res (Phila)* 6: 989-99.
300. Ning C, Wang HD, Gao R, Chang YC, Hu F, et al. (2018) Marine-derived protein kinase inhibitors for neuroinflammatory diseases. *Biomed Eng Online* 17: 46.
301. Wang J, Zheng J, Huang C, Zhao J, Lin J, et al. (2018) Eckmaxol, a phlorotannin extracted from *Ecklonia maxima*, produces anti- β -amyloid oligomer neuroprotective effects possibly via directly acting on glycogen synthase kinase 3 β . *ACS Chem Neurosci* 9: 1349-1356.
302. Zhou X, Yi M, Ding L, He S, Yan X (2019) Isolation and purification of a neuroprotective phlorotannin from the marine algae *Ecklonia maxima* by size exclusion and high-speed counter-current chromatography. *Mar Drugs* 17 pii: E212.
303. Rengasamy RRR, Mutalib AA, Ashwell RN, Wendy AS, Johannes VS (2013) Acetylcholinesterase inhibitory activity of phlorotannins isolated from the brown alga, *Ecklonia maxima* (Osbeck) Papenfuss. *Food Res Int* 54: 1250-1254.
304. Olasehinde TA, Olaniran AO, Okoh AI. (2019) Aqueous-ethanol extracts of some South African seaweed inhibit beta-amyloid aggregation, cholinesterases and beta-secretase activities *in vitro*. *J Food Biochem* 43:e12870.
305. Souza RB, Frota AF, Sousa RS, Cezario NA, Santos TB, et al. (2017) Neuroprotective effects of sulphated agaran from marine alga *Gracilaria cornea* in rat 6-hydroxydopamine Parkinson's disease model: Behavioral, neurochemical and transcriptional alterations. *Basic Clin Pharmacol Toxicol* 120: 159-170.
306. Liu T, Tang X, Jia X, Wu X, Huang M, et al. (2019) The complete plastid genome and phylogenetic analysis of *Gracilaria edulis*. *Mitochondrial DNA Part B* 4: 2598-2599.
307. Yang JI, Yeh CC, Lee JC, Yi SC, Huang HW, et al. (2012) Aqueous extracts of the edible *Gracilaria tenuistipitata* are protective against H₂O₂-induced DNA damage, growth inhibition and cell cycle arrest. *Molecules* 17: 7241-7254.
308. Natarajan S, Shanmugiahthevar KP, Kasi PD (2009) Cholinesterase inhibitors from *Sargassum* and *Gracilaria gracilis*: Seaweeds inhabiting South Indian coastal areas (Hare Island, Gulf of Mannar). *Nat Prod Res* 23: 355-369.
309. Ghannadi A, Plubrukarn A, Zandi K, Sartavi K, Yegdaneh A (2013) Screening for antimalarial and acetylcholinesterase inhibitory activities of some Iranian seaweeds. *Res Pharm Sci* 8:113-8.
310. Andriani Y, Syamsumir DF, Yee TC, Harisson FS, Heng GM, et al. (2016) Biological activities of isolated compounds from three edible Malaysian red seaweeds, *Gracilaria changii*, *G. manilaensis* and *Gracilaria* sp. *Nat Prod Commun* 11: 1117-1120.
311. Ghannadi A, Shabani L, Yegdaneh A (2016) Cytotoxic, antioxidant and phytochemical analysis of *Gracilaria* species from Persian Gulf. *Adv Biomed Res* 5: 139.
312. Olasehinde TA, Olaniran AO, Okoh AI (2019) Phenolic composition, antioxidant activity, anticholinesterase potential and modulatory effects of aqueous extracts of some seaweeds on β -amyloid aggregation and disaggregation. *Pharm Biol* 57: 460-469.
313. Hannan MA, Mohibullah M, Hong YK, Nam JH, Moon IS (2014) *Gelidium amansii* promotes dendritic spine morphology and synaptogenesis and modulates NMDA receptor-mediated postsynaptic current. *In Vitro Cell Dev Biol Anim* 50: 445-452.
314. Linares AF, Loikkanen J, Jorge MF, Soria RB, Novoa AV (2004) Antioxidant and neuroprotective activity of the extract from the seaweed, *Halimeda incrassata* (Ellis) Lamouroux, against *in vitro* and *in vivo* toxicity induced by methyl-mercury. *Vet Hum Toxicol* 46: 1-5.
315. Fallarero A, Loikkanen JJ, Männistö PT, Castañeda O, Vidal A (2003) Effects of aqueous extracts of *Halimeda incrassata* (Ellis) Lamouroux and *Bryothamnion*

- triquetrum* (S.G.Gmelin) Howe on hydrogen peroxide and methyl mercury-induced oxidative stress in GT1-7 mouse hypothalamic immortalized cells. *Phytomedicine* 10: 39-47.
316. Fallarero A, Peltoketo A, Loikkanen J, Tammela P, Vidal A, et al. (2006) Effects of the aqueous extract of *Bryothamnion triquetrum* on chemical hypoxia and aglycemia-induced damage in GT1-7 mouse hypothalamic immortalized cells. *Phytomedicine* 13: 240-245.
 317. Cavalcante-Silva LH, da Matta CB, de Araújo MV, Barbosa-Filho JM, de Lira DP, et al. (2012) Antinociceptive and anti-inflammatory activities of crude methanolic extract of red alga *Bryothamnion triquetrum*. *Mar Drugs* 10: 1977-92.
 318. Sánchez-Lamar Á, González-Pumariega M, Fuentes-León F, Vernhes Tamayo M, Schuch AP, et al. (2017) Evaluation of genotoxic and DNA photo-protective activity of *Bryothamnion triquetrum* and *Halimeda incrassata* seaweeds extracts. *Cosmetics* 4: 23.
 319. Liu J, Banskota AH, Critchley AT, Hafting J, Prithiviraj B (2015) Neuroprotective effects of the cultivated *Chondrus crispus* in a *C. elegans* model of Parkinson's disease. *Mar Drugs* 13: 2250-2266.
 320. Sangha JS, Wally O, Banskota AH, Stefanova R, Hafting JT, et al. (2015) A cultivated form of a red seaweed (*Chondrus crispus*), suppresses β -amyloid-induced paralysis in *Caenorhabditis elegans*. *Mar Drugs* 13: 6407-6424.
 321. Oh JH, Choi JS, Nam TJ (2018) Fucosterol from an edible brown alga *Ecklonia stolonifera* prevents soluble amyloid beta-induced cognitive dysfunction in aging rats. *Mar Drugs* 16 pii: E368.
 322. Yoon NY, Lee SH, Yong L, Kim SK (2009) Phlorotannins from *Ishige okamurae* and their acetyl- and butyryl cholinesterase inhibitory effects. *J Funct Foods* 1: 331-335.
 323. Dev K, Maurya R (2017) Marine derived anti-Alzheimer's agents of promise. In: Goutam Brahmachari. *Neuroprotective Natural Products: Clinical Aspects and Mode of Action*. John Wiley & Sons, ISBN 3527341862, 9783527341863.
 324. Tuppin P, Rivière S, Deutsch D, Gastaldi-Menager C, Sabaté JM (2019) Burden of drug use for gastrointestinal symptoms and functional gastrointestinal disorders in France: A national study using reimbursement data for 57 million inhabitants. *Ther Adv Gastroenterol* 12: 1756284819853790.
 325. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, et al. (2019) Burden and cost of gastrointestinal, liver and pancreatic diseases in the United States: Update 2018. *Gastroenterology* 156: 254-272.e11.
 326. Hu PJ (2015) Inflammatory bowel disease in Asia: The challenges and opportunities. *Intest Res* 13: 188-90.
 327. Werlang ME, Palmer WC, Lacy BE (2019) Irritable bowel syndrome and dietary interventions. *Gastroenterol Hepatol* (NY) 15: 16-26.
 328. AK Mohiuddin (2019) Complimentary treatments for minor GI disorders. *Adv Pharmacol Clin Trials* 4: 000153.
 329. Leung AK, Hon KL (2019) Gastroesophageal reflux in children: An updated review. *Drugs Context* 8: 212591.
 330. Brun R, Kuo B (2010) Functional dyspepsia. *Ther Adv Gastroenterol* 3: 145-164.
 331. Savarino E, de Bortoli N, Zentilin P, Martinucci I, Bruzzzone L, et al. (2012) Alginate controls heartburn in patients with erosive and nonerosive reflux disease. *World J Gastroenterol* 18: 4371-4378.
 332. Bharucha AE, Camilleri M, Veil E, Burton D, Zinsmeister AR (2013) Comprehensive assessment of gastric emptying with a stable isotope breath test. *Neurogastroenterol Motil* 25: e60-9.
 333. Bharucha AE, Kudva Y, Basu A, Camilleri M, Low PA, et al. (2015) Relationship between glycemic control and gastric emptying in poorly controlled type 2 diabetes. *Clin Gastroenterol Hepatol* 13: 466-476.
 334. KO SJ, Bu Y, Bae J, Bang YM, Kim J, et al. (2014) Protective effect of *Laminaria japonica* with probiotics on murine colitis. *Mediators Inflamm* 2014: 417814.
 335. Jing Y, Liu H, Xu W, Yang Q (2017) Amelioration of the DSS-induced colitis in mice by pretreatment with 4,4'-diaponeurosporene-producing *Bacillus subtilis*. *Exp Ther Med* 14: 6069-6073.
 336. Sudirman S, Hsu YH, He JL, Kong ZL (2018) Dietary polysaccharide-rich extract from *Eucheuma cottonii* modulates the inflammatory response and suppresses colonic injury on dextran sulfate sodium-induced colitis in mice. *PLoS One* 13: e0205252.
 337. Wardani G, Farida N, Andayani R, Kuntoro M, Sudjarwo SA (2017) The potency of red seaweed (*Eucheuma cottonii*) extracts as hepatoprotector on lead acetate-induced hepatotoxicity in mice. *Pharmacognosy Res* 9: 282-286.
 338. Xu SS, Liu QM, Xiao AF, Maleki SJ, Alcocer M, et al. (2017) *Eucheuma cottonii* sulfated oligosaccharides decrease food allergic responses in animal models by up-regulating regulatory T (Treg) cells. *J Agric Food Chem* 65: 3212-3222.

339. Peng J, Zheng TT, Li X, Liang Y, Wang LJ, et al. (2019) Plant-derived alkaloids: The promising disease-modifying agents for inflammatory bowel disease. *Front Pharmacol* 10: 351.
340. Carneiro JG, Holanda TBL, Quinderé ALG, Frota AF, Soares VVM, et al. (2018) Gastroprotective effects of sulphated polysaccharides from the alga *Caulerpa mexicana* reducing ethanol-induced gastric damage. *Pharmaceuticals (Basel)* 11 pii: E6.
341. Hernández-Muñoz R, Montiel-Ruiz C, Vázquez-Martínez O (2000) Gastric mucosal cell proliferation in ethanol-induced chronic mucosal injury is related to oxidative stress and lipid peroxidation in rats. *Lab Invest* 80: 1161-1169.
342. V Brito T, Barros FCN, Silva RO, Dias Júnior GJ, C Júnior JS, et al. (2016) Sulfated polysaccharide from the marine algae *Hypnea musciformis* inhibits TNBS-induced intestinal damage in rats. *Carbohydr Polym* 151: 957-964.
343. Lean QY, Eri RD, Fitton JH, Patel RP, Gueven N (2015) Fucoidan extracts ameliorate acute colitis. *PLoS One* 10: e0128453.
344. Nie Y, Lin Q, Luo F (2017) Effects of non-starch polysaccharides on inflammatory bowel disease. *Int J Mol Sci* 18 pii: E1372.
345. Ryan MT, O'Shea CJ, Collins CB, O'Doherty JV, Sweeney T (2012) Effects of dietary supplementation with *Laminaria hyperborea*, *Laminaria digitata* and *Saccharomyces cerevisiae* on the IL-17 pathway in the porcine colon. *J Anim Sci* 90: 263-265.
346. Shimazu T, Borjigin L, Katoh K, Roh SG, Kitazawa H, et al. (2019) Addition of Wakame seaweed (*Undaria pinnatifida*) stalk to animal feed enhances immune response and improves intestinal microflora in pigs. *Anim Sci J* 90: 1248-1260.
347. O'Sullivan L, Murphy B, McLoughlin P, Duggan P, Lawlor PG, et al. (2010) Prebiotics from marine macroalgae for human and animal health applications. *Mar Drugs* 8: 2038-2064.
348. Jha R, Fohse JM, Tiwari UP, Li L, Willing BP (2019) Dietary fiber and intestinal health of monogastric animals. *Front Vet Sci* 6:48.
349. de Jesus Raposo MF, de Moraes AM, de Moraes RM (2016) Emergent sources of prebiotics: Seaweeds and microalgae. *Mar Drugs* 14 pii: E27.
350. Ko SJ, Kim J, Han G, Kim SK, Kim HG, et al. (2014) *Laminaria japonica* combined with probiotics improves intestinal microbiota: A randomized clinical trial. *J Med Food* 17: 76-82.
351. Shahid MA, Sharma S (2019) Physiology, thyroid hormone. [Updated 2019 Mar 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Available from: <https://www.ncbi.nlm.nih.gov/books/NBK500006/>
352. Combet E, Ma ZF, Cousins F, Thompson B, Lean ME (2014) Low-level seaweed supplementation improves iodine status in iodine-insufficient women. *Br J Nutr* 112: 753-61.
353. Bajaj JK, Salwan P, Salwan S (2016) Various possible toxicants involved in thyroid dysfunction: A review. *J Clin Diagn Res* 10: FE01-3.
354. Farebrother J, Zimmermann MB, Andersson M (2019) Excess iodine intake: Sources, assessment and effects on thyroid function. *Ann N Y Acad Sci* 1446: 44-65.
355. Wang C, Yatsuya H, Li Y, Ota A, Tamakoshi K, et al. (2016) Prospective study of seaweed consumption and thyroid cancer incidence in women: The Japan collaborative cohort study. *Eur J Cancer Prev.* 25: 239-45.
356. Chen A, Kim SS, Chung E, Dietrich KN (2013) Thyroid hormones in relation to lead, mercury and cadmium exposure in the National Health and Nutrition Examination Survey, 2007-2008. *Environ Health Perspect* 121: 181-6.
357. Buha A, Matovic V, Antonijevic B, Bulat Z, Curcic M, et al. (2018) Overview of cadmium thyroid disrupting effects and mechanisms. *Int J Mol Sci* 19 pii: E1501.
358. Nie X, Chen Y, Chen Y, Chen C, Han B, et al. (2017) Lead and cadmium exposure, higher thyroid antibodies and thyroid dysfunction in Chinese women. *Environ Pollut* 230: 320-328.
359. Yorita Christensen KL (2013) Metals in blood and urine and thyroid function among adults in the United States 2007-2008. *Int J Hyg Environ Health* 216: 624-32.
360. Zava TT, Zava DT (2011) Assessment of Japanese iodine intake based on seaweed consumption in Japan: A literature-based analysis. *Thyroid Res* 4: 14.
361. Myers SP, Mulder AM, Baker DG, Robinson SR, Rolfe MI, et al. (2016) Effects of fucoidan from *Fucus vesiculosus* in reducing symptoms of osteoarthritis: A randomized placebo-controlled trial. *Biologics* 10: 81-88.
362. Myers SP, O'Connor J, Fitton JH, Brooks L, Rolfe M, et al. (2010) A combined phase I and II open label study on the effects of a seaweed extract nutrient complex on osteoarthritis. *Biologics* 4: 33-44.
363. Brown ES, Allsopp PJ, Magee PJ, Gill CI, Nitecki S, et al. (2014) Seaweed and human health. *Nutr Rev* 72: 205-16.

364. Cardoso LCP, Pinto NB, Nobre MEP, Silva MR, Pires GM, et al. (2019) Anti-inflammatory and antinociceptive effects of phonophoresis in animal models: A randomized experimental study. *Braz J Med Biol Res* 52: e7773.
365. Bhatia S, Sharma K, Sharma A, Nagpal K, Bera T (2015) Anti-inflammatory, analgesic and antiulcer properties of *Porphyra vietnamensis*. *Avicenna J Phytomed* 5: 69-77.
366. Bhatia S, Sardana S, Senwar KR, Dhillon A, Sharma A, et al. (2019) *In vitro* antioxidant and antinociceptive properties of *Porphyra vietnamensis*. *Biomedicine (Taipei)* 9: 3.
367. Zakaria A, Jais MR, Ishak R (2018) Analgesic Properties of *Nigella Sativa* and *Eucheuma Cottonii* Extracts. *J Nat Sci Biol Med* 9: 23-26.
368. Vázquez AI, Sánchez CM, Delgado NG, Alfonso AM, Ortega YS, et al. (2011) Anti-inflammatory and analgesic activities of red seaweed *Dichotomaria obtusata*. *Braz J Pharm Sci* 47: 111-8.
369. Abdelhamid A, Jouini M, Bel Haj Amor H, Mzoughi Z, Dridi M, et al. (2018) Phytochemical analysis and evaluation of the antioxidant, anti-inflammatory and antinociceptive potential of phlorotannin-rich fractions from three mediterranean brown seaweeds. *Mar Biotechnol (NY)* 20: 60-74.
370. Kim S, Choi SI, Kim GH, Imm JY (2019) Anti-inflammatory effect of ecklonia cava extract on *Porphyromonas gingivalis* lipopolysaccharide-stimulated macrophages and a periodontitis rat model. *Nutrients* 11 pii: E1143.
371. Ha JW, Song H, Hong SS, Boo YC (2019) Marine alga *Ecklonia cava* extract and dieckol attenuate prostaglandin E(2) production in HaCaT keratinocytes exposed to airborne particulate matter. *Antioxidants (Basel)* 8 pii: E190.
372. Kim JG, Lim DW, Cho S, Han D, Kim YT (2014) The edible brown seaweed *Ecklonia cava* reduces hypersensitivity in postoperative and neuropathic pain models in rats. *Molecules* 19: 7669-78.
373. de Souza ET, de Lira DP, de Queiroz AC, da Silva DJ, de Aquino AB, et al. (2009) The antinociceptive and anti-inflammatory activities of caulerpin, a bisindole alkaloid isolated from seaweeds of the genus *Caulerpa*. *Mar Drugs* 7: 689-704.
374. Shih CC, Hwang HR, Chang CI, Su HM, Chen PC, et al. (2017) Anti-inflammatory and antinociceptive effects of ethyl acetate fraction of an edible red macroalgae *Sarcodia ceylanica*. *Int J Mol Sci* 18 pii: E2437.
375. Sayed AA, Sadek SA, Solimán AM, Marzouk M (2016) Prospective effect of red algae, *Actinotrichia fragilis*, against some osteoarthritis etiology. *Afr J Tradit Complement Altern Med* 14: 231-241.
376. Albuquerque IR, Cordeiro SL, Gomes DL, Dreyfuss JL, Filgueira LG, et al. (2013) Evaluation of antinociceptive and anti-inflammatory activities of a heterofucan from *Dictyota menstrualis*. *Mar Drugs* 11:2722-40.
377. Coura CO, de Araújo IW, Vanderlei ES, Rodrigues JA, Quinderé AL, et al. (2012) Antinociceptive and anti-inflammatory activities of sulphated polysaccharides from the red seaweed *Gracilaria cornea*. *Basic Clin Pharmacol Toxicol* 110: 335-41.
378. de Sousa Oliveira Vanderlei E, de Araújo IW, Quinderé AL, Fontes BP, Eloy YR, et al. (2011) The involvement of the HO-1 pathway in the anti-inflammatory action of a sulfated polysaccharide isolated from the red seaweed *Gracilaria birdiae*. *Inflamm Res* 60: 1121-30.
379. Florez N, Gonzalez-Munoz MJ, Ribeiro D, Fernandes E, Dominguez H, et al. (2017) Algae polysaccharides' chemical characterization and their role in the inflammatory process. *Curr Med Chem* 24: 149-175.
380. Wang L, Wang X, Wu H, Liu R (2014) Overview on biological activities and molecular characteristics of sulfated polysaccharides from marine green algae in recent years. *Mar Drugs* 12: 4984-5020.
381. da Conceição Rivanor RL, Chaves HV, do Val DR, de Freitas AR, Lemos JC, et al. (2014) A lectin from the green seaweed *Caulerpa cupressoides* reduces mechanical hyper-nociception and inflammation in the rat temporomandibular joint during zymosan-induced arthritis. *Int Immunopharmacol* 21: 34-43.
382. Margret RJ, Kumaresan S, Ravikumar S (2009) A preliminary study on the anti-inflammatory activity of methanol extract of *Ulva lactuca* in rat. *J Environ Biol* 30(5 Suppl): 899-902.
383. Neelakandan Y, Venkatesan A (2016) Antinociceptive and anti-inflammatory effect of sulfated polysaccharide fractions from *Sargassum wightii* and *Halophila ovalis* in male Wistar rats. *Indian J Pharmacol* 48: 562-570.
384. Kim DH, Kim ME, Lee JS (2015) Inhibitory effects of extract from *G. lanceolata* on LPS-induced production of nitric oxide and IL-1 β via down-regulation of MAPK in macrophages. *Appl Biochem Biotechnol* 175: 657-65.
385. Kang JY, Khan MN, Park NH, Cho JY, Lee MC, et al. (2008) Antipyretic, analgesic and anti-inflammatory activities of the seaweed *Sargassum fulvellum* and *Sargassum thunbergii* in mice. *J Ethnopharmacol* 116: 187-90.

386. Lin YY, Lin SC, Feng CW, Chen PC, Su YD, et al. (2015) Anti-inflammatory and analgesic effects of the marine-derived compound excavatolide B isolated from the culture-type formosan gorgonian *Briareum excavatum*. *Mar Drugs* 13: 2559-79.
387. Ribeiro NA, Abreu TM, Chaves HV, Bezerra MM, Monteiro HS, et al. (2014) Sulfated polysaccharides isolated from the green seaweed *Caulerpa racemosa* plays antinociceptive and anti-inflammatory activities in a way dependent on HO-1 pathway activation. *Inflamm Res* 63: 569-580.
388. Hwang PA, Hung YL, Chien SY (2015) Inhibitory activity of *Sargassum hemiphyllum* sulfated polysaccharide in arachidonic acid-induced animal models of inflammation. *J Food Drug Anal* 23: 49-56.
389. Lajili S, Deghrigue M, Bel Haj Amor H, Muller CD, Bouraoui A (2016) *In vitro* immunomodulatory activity and *in vivo* anti-inflammatory and analgesic potential with gastroprotective effect of the Mediterranean red alga *Laurencia obtusa*. *Pharm Biol* 54: 2486-2495.
390. Matta, CBB, Cavalcante-Silva LHA, Araújo-Júnior JX, Miranda GEC, et al. (2015) Antinociceptive and anti-inflammatory effects of *Caulerpa kempfii* Caulerpacae. *Rev Virtual Quim* 7: 730-743.
391. Rodrigues JA, Vanderlei ES, Silva LM, Araújo IW, Queiroz IN, et al. (2012) Antinociceptive and anti-inflammatory activities of a sulfated polysaccharide isolated from the green seaweed *Caulerpa cupressoides*. *Pharmacol Rep* 64: 282-292.
392. Frost I, Van Boeckel TP, Pires J, Craig J, Laxminarayan R (2019) Global geographic trends in antimicrobial resistance: The role of international travel. *J Travel Med* pii: taz036.
393. Dixit A, Kumar N, Kumar S, Trigun V (2019) Antimicrobial resistance: Progress in the decade since emergence of New Delhi metallo- β -lactamase in India *Indian J Community Med* 44: 4-8.
394. Lu WJ, Lin HJ, Hsu PH, Lai M, Chiu JY, et al. (2019) Brown and red seaweeds serve as potential efflux pump inhibitors for drug-resistant *Escherichia coli*. *Evid Based Complement Alternat Med* 2019: 1836982.
395. Alves C, Silva J, Pinteus S, Gaspar H, Alpoim MC, et al. (2018) From marine origin to therapeutics: The antitumor potential of marine algae-derived compounds. *Front Pharmacol* 9: 777.
396. Besednova N, Zaporozhets T, Kuznetsova T, Makarenkova I, Fedyanina L, et al. (2019) Metabolites of seaweeds as potential agents for the prevention and therapy of influenza infection. *Mar Drugs* 17 pii: E373.
397. Pérez MJ, Falqué E, Domínguez H (2016) Antimicrobial action of compounds from marine seaweed. *Mar Drugs* 14 pii: E52.
398. Walsh PJ, McGrath S, McKelvey S, Ford L, Sheldrake G, et al. (2019) The osteogenic potential of brown seaweed extracts. *Mar Drugs* 17 pii: E141.
399. Jacobsen C, Sørensen AM, Holdt SL, Akoh CC, Hermund DB (2019) Source, extraction, characterization and applications of novel antioxidants from seaweed. *Annu Rev Food Sci Technol* 10: 541-568.
400. Chakraborty K, Dhara S (2019) First report of substituted 2H-pyranoids from brown seaweed *Turbinaria conoides* with antioxidant and anti-inflammatory activities. *Nat Prod Res* 5: 1-11.
401. Farasat M, Khavari-Nejad RA, Nabavi SM, Namjooyan F (2014) Antioxidant activity, total phenolics and flavonoid contents of some edible green seaweed from northern coasts of the Persian Gulf. *Iran J Pharm Res. Winter* 13:163-70.
402. Silva J, Alves C, Freitas R, Martins A, Pinteus S, et al. (2019) Antioxidant and neuroprotective potential of the brown seaweed *Bifurcaria bifurcata* in an *in vitro* Parkinson's disease model. *Mar Drugs* 17 pii: E85.
403. Cho SH, Kang SE, Cho JY, Kim AR, Park SM, et al. (2007) The antioxidant properties of brown seaweed (*Sargassum siliquastrum*) extracts. *J Med Food* 10: 479-485.
404. Pinteus S, Silva J, Alves C, Horta A, Fino N, et al. (2017) Cytoprotective effect of seaweeds with high antioxidant activity from the Peniche coast (Portugal). *Food Chem* 218: 591-599.
405. Sivagnanam SP, Yin S, Choi JH, Park YB, Woo HC, et al. (2015) Biological properties of fucoxanthin in oil recovered from two brown seaweeds using supercritical CO₂ extraction. *Mar Drugs* 13: 3422-42.
406. Saravana PS, Cho YJ, Park YB, Woo HC, Chun BS (2016) Structural, antioxidant and emulsifying activities of fucoidan from *Saccharina japonica* using pressurized liquid extraction. *Carbohydr Polym* 153: 518-525.
407. Athiperumalsami T, Rajeswari VD, Poorna SH, Kumar V, Jesudass LL (2010) Antioxidant activity of seagrasses and seaweeds. *Bot* 53: 251-257.
408. Kar K, Sahoo SS, Kar B, Naik SK, Panda PC (2019) Antioxidant activity of *Halophila ovalis* and *Halophila beccarii* (Hydrocharitaceae): Two important seagrass species of Chilika lagoon, India. *Asian J Pharm Clin Res* 12: 136-40.
409. Ammar HH, Hafsa J, Le Cerf D, Bouraoui A, Majdoub H (2016) Antioxidant and gastroprotective activities of

- polysaccharides from the Tunisian brown algae (*Cystoseira sedoides*). J Tunisian Chem Soc 18: 80-88.
410. Mhadhebi L, Laroche-Clary A, Robert J, Bouraoui A (2011) Antioxidant, anti-inflammatory and antiproliferative activities of organic fractions from the Mediterranean brown seaweed *Cystoseira sedoides*. Can J Physiol Pharmacol 89: 911-21.
 411. Murugan K, Iyer VV (2013) Differential growth inhibition of cancer cell lines and antioxidant activity of extracts of red, brown and green marine algae. In vitro Cell Dev Biol Anim 49: 324-34.
 412. Lee JW, Seok JK, Boo YC (2018) *Ecklonia cava* extract and dieckol attenuate cellular lipid peroxidation in keratinocytes exposed to PM10. Evid Based Complement Altern Med 2018: 8248323.
 413. Athukorala Y, Kim KN, Jeon YJ (2006) Antiproliferative and antioxidant properties of an enzymatic hydrolysate from brown alga, *Ecklonia cava*. Food Chem Toxicol 44: 1065-74.
 414. Dong X, Bai Y, Xu Z, Shi Y, Sun Y, et al. (2019) Phlorotannins from *Undaria pinnatifida* sporophyll: Extraction, antioxidant and anti-inflammatory activities. Mar Drugs 17 pii: E434.
 415. Mesripour A, Rabian N, Yegdaneh A (2019) The effect of different partitions of seaweed *Sargassum plagyophyllum* on depression behavior in mice model of despair. J Complement Integr Med.
 416. Farmer MA, Leja A, Foxen-Craft E, Chan L, MacIntyre LC, et al. (2014) Pain reduces sexual motivation in female but not male mice. J Neurosci 34: 5747-5753.
 417. Mahadevan K (2018) Seaweeds: A sustainable food source. In: Sirpa Sarlio. Towards Healthy and Sustainable Diets: Perspectives and Policy to Promote the Health of People and the Planet Springer Briefs in Public Health. Publisher: Springer ISBN 3319742043, 9783319742045.
 418. Ciju RJ (2019) Seaweeds as vegetables. Publisher: AGRIHORTICO.
 419. Philippines. Ministry of Natural Resources (1986) Guide to Philippine Flora and Fauna, Volume 1. Guide to Philippine Flora and Fauna, Natural Resources Management Center (Filipinas). Publisher: Natural Resources Management Center, Ministry of Natural Resources: University of the Philippines, ISBN 9711026198, 9789711026196
 420. Liu X, Wang S, Cao S, He X, Qin L, et al. (2018) Structural characteristics and anticoagulant property *in vitro* and *in vivo* of a seaweed sulfated rhamnan. Mar Drugs 16 pii: E243.
 421. Adrien A, Bonnet A, Dufour D, Baudouin S, Maugard T, et al. (2019) Anticoagulant activity of sulfated Ulvan isolated from the green macroalga *Ulva rigida*. Mar Drugs 17 pii: E291.
 422. Mendes Marques ML, Presa FB, Viana RLS, Costa MSSP, Amorim MOR, et al. (2018) Anti-thrombin, anti-adhesive, anti-migratory and anti-proliferative activities of sulfated galactans from the tropical green seaweed, *Udotea flabellum*. Mar Drugs 17 pii: E5.
 423. Jiao G, Yu G, Zhang J, Ewart HS (2011) Chemical structures and bioactivities of sulfated polysaccharides from marine algae. Mar Drugs 9: 196-223.
 424. Carvalhal F, Cristelo RR, Resende DISP, Pinto MMM, Sousa E, et al. (2019) Antithrombotics from the sea: Polysaccharides and beyond. Mar Drugs 17 pii: E170.
 425. He X, Zang J, Liao P, Zheng Y, Lu Y, et al. (2019) Distribution and dietary predictors of urinary phthalate metabolites among pregnant women in Shanghai, China. Int J Environ Res Public Health 16 pii: E1366.
 426. Gomes DL, Melo KRT, Queiroz MF, Batista LANC, Santos PC, et al. (2019) *In vitro* studies reveal antiurolithic effect of antioxidant sulfated polysaccharides from the green seaweed *Caulerpa cupressoides* var. *flabellata*. Mar Drugs 17 pii: E326.
 427. Kang JI, Kim SC, Han SC, Hong HJ, Jeon YJ, et al. (2012) Hair-loss preventing effect of *Grateloupia elliptica*. Biomol Ther (Seoul) 20: 118-124.
 428. Machado LP, Matsumoto ST, Jamal CM, da Silva MB, Centeno Dda C, et al. (2014) Chemical analysis and toxicity of seaweed extracts with inhibitory activity against tropical fruit anthracnose fungi. J Sci Food Agric 94: 1739-1744.
 429. El Amrani Zerrifi S, Tazart Z, El Khalloufi F, Oudra B, Campos A, et al. (2019) Potential control of toxic cyanobacteria blooms with Moroccan seaweed extracts. Environ Sci Pollut Res Int 26: 15218-15228.