Review

The Use of Invasive Algae Species as a Source of Secondary Metabolites and Biological Activities: Spain as Case-Study

Antia G. Pereira 1,2,*, Maria Fraga-Corral 1,2,*, Paula Garcia-Oliveira 1,2,*, Catarina Lourenço-Lopes 1,*, Maria Carpena 1,*, Miguel A. Prieto 1,2,*, and Jesus Simal-Gandara 1,*

1 Nutrition and Bromatology Group, Department of Analytical and Food Chemistry, Faculty of Food Science and Technology, University of Vigo, Ourense Campus, E3204 Ourense, Spain; antia.gonzalez.pereira@uvigo.es (A.G.P.); maria.fraga.corral@hotmail.es (M.F.-C.); paula.garcia.oliveira@uvigo.es (P.G.-O.); c.lopes@uvigo.es (C.L.-L.); maria.carpena.rodriguez@uvigo.es (M.C.)
2 Centro de Investigación de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolonia, 5300-253 Bragança, Portugal
* Correspondence: mprieto@uvigo.es (M.A.P.); jsimal@uvigo.es (J.S.-G.)

Abstract: In the recent decades, algae have proven to be a source of different bioactive compounds with biological activities, which has increased the potential application of these organisms in food, cosmetic, pharmaceutical, animal feed, and other industrial sectors. On the other hand, there is a growing interest in developing effective strategies for control and/or eradication of invasive algae since they have a negative impact on marine ecosystems and in the economy of the affected zones. However, the application of control measures is usually time and resource-consuming and not profitable. Considering this context, the valorization of invasive algae species as a source of bioactive compounds for industrial applications could be a suitable strategy to reduce their population, obtaining both environmental and economic benefits. To carry out this practice, it is necessary to evaluate the chemical and the nutritional composition of the algae as well as the most efficient methods of extracting the compounds of interest. In the case of northwest Spain, five algae species are considered invasive: *Asparagopsis armata*, *Codium fragile*, *Gracilaria vermiculophylla*, *Sargassum muticum*, and *Grateloupia turuturu*. This review presents a brief description of their main bioactive compounds, biological activities, and extraction systems employed for their recovery. In addition, evidence of their beneficial properties and the possibility of use them as supplement in diets of aquaculture animals was collected to illustrate one of their possible applications.

Keywords: seaweeds; aquaculture feed; invasive macroalgae species; biological activity; metabolites

1. Introduction

Invasive alien species (IAS), also known as exotic or non-native species, are plants or animals that have been introduced, intentionally or not, into regions where it is not usual to find them [1,2]. This situation often leads to negative consequences for the new host ecosystem, generally related to the community biodiversity reduction, changes in the abundance of the species and in the population’s configuration across the habitats, as well as trophic displacements that can trigger other cascade effects [3]. Spanish law 42/2007, of 13 December, on Natural Heritage and Biodiversity, defines IAS as “species that are introduced and established in an ecosystem or natural habitat, which are an agent of change and a threat to native biological diversity, either by their invasive behavior, or by the risk of genetic contamination”. IAS usually present high growth and reproduction rates, the ability to prosper in different environments, the capacity to use several food sources, and the ability to tolerate a wide range of environmental conditions. All these factors, along with the lack of natural predators, make these organisms more difficult to control and allow them to succeed in colonizing new ecosystems [3,4]. In addition, these species may feed on natural species or may carry pathogens for native organisms and even...
humans [5]. The invasion of non-native species also entails economic cost, which have been estimated at $1.4 trillion in the last decade [6].

Among marine IAS declared in Europe, around 20–40% are macroalgae (seaweeds) [7], a term that refers to several species of multicellular and macroscopic marine algae, including different types of Chlorophyta (green), Phaeophyta (brown), and Rhodophyta (red) macroalgae. Non-native seaweeds are particularly prone to become invasive due to their high reproductive rates, the production of toxic metabolites, and their perennial status that makes them more competitive than native species [1]. Several species periodically become a major problem, causing red tides, fouling nets, clogging waterways, and changing nutrient regimes in areas near to fisheries, aquaculture systems, and desalination facilities [1,4].

In the last years, the presence of invasive macroalgae in the northwestern marine areas of Spain has become a common problem due to growing globalization, climate change, aquaculture, fisheries, and marine tourism [8]. However, their proliferation could also offer new opportunities since the recovery of the algal biomass and their novel applications in different economic sectors could increase their added value. Obtaining natural compounds with biological properties of interest for both the food and the pharmaceutical industries is one of these possible applications. The aim of the present work is to summarize the existing knowledge about the bioactive compounds of the principal invasive species affecting the Galician coasts (northwest Spain).

2. Possible Exploitation of the Invasive Species

The exploitation of macroalgae is a growing industry with several applications, including human food and animal feed, biorefinery, fertilizers, production of phycocolloids, and obtaining compounds with biological properties [6,9]. Several applications are briefly discussed below.

2.1. Food Industry

Macroalgae have been consumed since ancient times in many countries around the world, mainly in the Asian regions. Nevertheless, their consumption has increased in the last decades in western countries, which has been attributed to the high nutritional values of macroalgae and their health benefits [10,11]. Some of the most consumed macroalgae are nori or purple laver (Porphyra spp.), kombu (Laminaria japonica), wakame (Undaria pinnatifida), Hiziki (Hizikia fusiforme), or Irish moss (Chondrus crispus), which can be consumed in different food formats (salads, soups, snacks, pasta, etc.) [11,12]. Still, most of them are considered an innovative niche product. Macroalgae are also widely used in the food industry to produce phycocolloids (polysaccharides of high molecular weight composed mostly of simple sugars), mainly alginates, agars, and carrageenans, which are frequently used as thickeners, stabilizers, as well as for probiotics encapsulation, gels, and water-soluble films formation [6,13]. Furthermore, diverse molecules present in algae have been shown to exert several bioactivities, such as antioxidant, anti-inflammatory, antimicrobial, and antiviral effects. These bioactive compounds (mainly proteins, polyunsaturated fatty acids, carotenoids, vitamins, and minerals) may play important roles in functional foods (e.g., dairy products, desserts, pastas, oil derivatives, or supplements) with favorable outcomes on human health [14]. Other applications of algae in the food industry include their use as colorant agents and the extraction of valuable oils (such as eicosapentaenoic acid, docosahexaenoic acid, and arachidonic acid) [15].

2.2. Biofuel

The development of algal biofuels (“third-generation biofuels”) has been considered an option to reduce the use of petroleum-based fuels and avoid competition between food and energy production for arable soil, since macroalgae grow in water. These organisms do not contain lignin, thus they are good substrates for biogas production in anaerobic digesters, while fermentable carbohydrates are fit for bioethanol production. Although the production of bioenergy from macroalgae is not economically feasible nowadays, several
measures have been proposed to achieve a rational production cost in the future [16]. On the other hand, microalgae are considered a more suitable source to produce biodiesel due to the greater ease of controlling the life cycle and increasing the reproduction rate [17]. Microalgae biomass can be used for electricity generation or biofuel production after the lipid extraction. It has shown 80% of the average energy content of petroleum. The lipid content is highly dependent on the microalgae species and the cultivation conditions, thus not all species will be profitable, and choosing appropriate microalga strain is crucial [18]. Some microalgae used to produce biofuel are *Chlorella* spp., *Dunaliella salina, Haematococcus pluvialis, Spirulina platensis, Porphyridium cruentum, Microcystis aeruginosa,* and *Scenedesmus obliquus* [19].

2.3. Therapeutic and Cosmetic Products

The use of macroalgae for therapeutic purposes has a long history, but the search for biologically active substances from these organisms is quite recent. Numerous studies have demonstrated the biological properties of macroalgae extracts and compounds, including antioxidant, anti-inflammatory [20], antithrombotic, anticoagulant and coagulant [21], antimicrobial [22], and anticancer [23]. In addition, macroalgae have been demonstrated to exert biological properties applicable to cosmetic products, such as photo-protection, anti-aging, or anti-cellulite (Table 1). Considering this range of activities, macroalgae extracts and compounds have been considered for different pharmacologic and cosmetic products [24]. Regarding cosmetics, brown and red seaweeds are usually employed. The interest of these species lies in their content in cosmeceuticals ingredients, such as phlorotannins, polysaccharides, and carotenoid pigments [25]. These compounds are incorporated into cosmetics due to their bioactivities, their capacity to improve organoleptic properties, and their capacity to stabilize and preserve the products [26].

| Treatment | Specie | Compound | Result | Ref. |
|-----------|--------|----------|--------|-----|
| Skin aging | *Alaria esculenta* | Extract | Decline the amount of progerin in aged fibroblasts at the lowest tested concentration (not for younger cells) | [27] |
| | *Phaeodactylum tricornutum* | Ethanol extract | Protecting the skin from the adverse effects of UV exposure; preventing and/or delaying the appearance of skin aging effects | [28] |
| | *Hizikia fusiformis* | Fucosterol | Inhibit metalloproteinase-1 expression | [29] |
| | *Ecklonia stolonifera* | Phlorotannins | Inhibit metalloproteinase-1 expression | [30] |
| Sunscreen | *Halidrys siliquosa* | Phlorotannins | UV-filter activity | [31] |
| | Brown seaweeds | Phlorotannins | Protective effect against photo-oxidative stress | [32] |
| | *Corallina pilulifera* | Phenolic compounds | Anti-photoaging activity and inhibition of matrix metalloproteinase | [33] |
| | *Sargassum* spp. | Fucoxanthin | Protective effect on UV-B induced cell damage | [34] |
| | *Sargassum confusum* | Fucoidan | Suppress photo-oxidative stress and skin barrier perturbation in UVB-induced human keratinocytes | [35] |
| Moisturizer | *Macrocystis pyrifera, Porphyra columbina* | Acetone extracts | In vivo UVB-photoprotective activity | [36] |
| | *Fucus vesiculosus* | Fucoidan | Inhibition of hyaluronidase enzyme | [37] |
| | *Laminaria japonica* | 5% water:propylene glycol (50:50) extracts | Hydration with the alga extract increased by 14.44% compared with a placebo | [38] |
| | *Rhizoclonium hieroglyphicum* | Polysaccharides and amino acids | Similar moisturizing effects to hyaluronic acid and glycerin | [39] |
| Whitening | *Nannochloropsis oculata* | Zeaxanthin | Antityrosinase activity | [40] |
| | *Laminaria japonica* | Fucoxanthin | Antityrosinase activity | [41] |
| | *Arthrospira platensis* | Ethanol extract | Antityrosinase activity | [42] |
| Hair care | *Chlorella* spp. | Intact microalgae cells | Soften and make flexible both skin and hair | [43] |
| | *Ecklonia cava* | Dioxinodihydroxecol | Promote hair growth | [44] |
2.4. Fertilizer and Animal Feed

Currently, the negative environmental impacts of synthetic fertilizers have been identified. Thus, the use of organic fertilizers, including macroalgae, has been proposed as a suitable alternative to reduce the impact on the environment [45,46]. In fact, macroalgae have been used since ancient times as fertilizers, and several beneficial effects have been described, such as enhancement of crops growth and yield, increased resistance against abiotic and biotic stresses, or nutrient intake [46–48]. The biostimulant effects of macroalgae have been attributed to diverse biological compounds such as plant hormones, phlorotannins, and oligosaccharides [48].

Regarding animal feed, macroalgae have been employed for this purpose since ancient times as feed but also as nutritious supplements [49]. Several studies have evaluated the positive effects of macroalgae-enriched food, both for terrestrial animals [50] and specially in aquaculture animals [51–54].

3. Main Invasive Species of Northwest Spain and Their Bioactive Compounds

According to the Spanish Catalogue of IAS of Algae [55], there are 14 species of invasive seaweeds in Spain which can be divided into: (i) red species: Acrothamnion preissii, Asparagopsis armata, Asparagopsis taxiformis, Grateloupia turuturu, Lophocladia lallemandii, and Womersleyella setacea; (ii) brown species: Gracilaria vermiculophylla, Sargassum muticum, Stypopodium schirmeri, and Undaria pinnatifida; and (iii) green species: Caulerpa taxifolia, Codium fragile, and Caulerpa racemosa. In addition, there are also invasive diatoms, such as the Didymosphenia geminata, also known as rock snot or didymo (Table 2). However, it should be noted that this catalogue is a dynamic instrument subjected to continuous changes and updating. Most of these invasive species are originally from the Indo-Pacific Ocean (Western Australia, New Zealand, and Japan), and it is thought that they have been introduced into the Spanish coasts through the Suez Canal. Maritime traffic, ballast water, fishing nets, trade of oysters, aquaculture, and fouling are considered the main routes of dispersion [8,56–58].

Table 2. Invasive algae species in Spain: taxonomy, origin, geographical distribution, and principal uses.

| Specie                     | Taxonomy                                      | Native Distribution     | Distribution in Spain | Other Regions in Which They Are Invasive                      | Principal Uses                      |
|----------------------------|-----------------------------------------------|-------------------------|-----------------------|---------------------------------------------------------------|-------------------------------------|
| Acrothamnion preissii      | Phylum: Rhodophyta Class: Florideophyceae     | Western Australia       | All Spain             | Temperate coastlines on the Pacific coast of North America and western coasts of Europe | - Unknown                          |
| Asparagopsis armata        | Phylum: Rhodophyta Class: Bonnemasioniales    | Indo-Pacific Ocean      | All Spain             | Mediterranean, Portugal, and Ireland                          | - Pharmaceutical potential as antibiotic |
| Asparagopsis taxiformis    | Phylum: Rhodophyta Class: Nemaliales Family: Bonnemaisoniacae | Australia and New Zealand | Except Canarias  | Portugal                                                      | - Human consumption - Antifungal     |
| Grateloupia turuturu       | Phylum: Rhodophyta Class: Halymiinales Family: Halymiinales | Pacific Ocean           | All Spain             | North America, Europe, and Oceania                           | - Human consumption - Fertilizer     |
| Lophocladia lallemandii    | Phylum: Rhodophyta Class: Florideophyceae    | Indo-Pacific Ocean      | All Spain             | Mediterranean                                                  | - Unknown                           |
| Womersleyella setacea      | Phylum: Rhodophyta Class: Florideophyceae    | Indo-Pacific Ocean      | All Spain             | Mediterranean                                                  | - Unknown                           |


Table 2. Cont.

| Specie                  | Taxonomy                      | Native Distribution       | Distribution in Spain | Other Regions in Which They Are Invasive | Principal Uses                        |
|-------------------------|-------------------------------|----------------------------|-----------------------|------------------------------------------|---------------------------------------|
| **Brown species**       |                               |                            |                       |                                          |                                       |
| *Gracilaria vermiculophylla* | Phylum: Rhodophyta             | North-east Pacific         | All Spain             | Europe and North America                 | - Animal feed                        |
|                         | Class: Florideophyceae         |                            |                       |                                          | - Biocatalysts                        |
|                         | Orden: Gracilariales           |                            |                       |                                          | - Fertilizer                          |
|                         | Family: Gracilariaceae         |                            |                       |                                          | - Human consumption                   |
| *Sargassum muticum*     | Phylum: Ochrophyta             | Indo-Pacific Ocean         | All Spain             | Pacific Coast of North America, North Sea, Portugal, and the Mediterranean | - Animal feed                        |
|                         | Class: Phaeophyceae            |                            |                       |                                          | - Food additive                       |
|                         | Order: Fucales                |                            |                       |                                          | - Pesticide                           |
|                         | Family: Sargassaceae           |                            |                       |                                          |                                       |
| *Stypopodium schimperi* | Phylum: Ochrophyta             | Indo-Pacific Ocean and Red Sea | All Spain             | Africa and Southwest Asia                | - Unknown                             |
|                         | Class: Phaeophyceae            |                            |                       |                                          |                                       |
|                         | Order: Dictyotales             |                            |                       |                                          |                                       |
|                         | Family: Dictyotaceae           |                            |                       |                                          |                                       |
| *Undaria pinnatifida*   | Phylum: Heterokontophyta       | Asia                       | All Spain             | Europe                                  | - Human consumption                   |
|                         | Class: Phaeophyceae            |                            |                       |                                          | - Animal feed                         |
|                         | Order: Laminariales            |                            |                       |                                          |                                       |
|                         | Family: Alariaceae             |                            |                       |                                          |                                       |
| **Green species**       |                               |                            |                       |                                          |                                       |
| *Caulerpa taxifolia*    | Phylum: Chlorophyta            | Tropical area              | All Spain             | Mediterranean, California, and southern Australia | - Laboratory use                      |
|                         | Class: Bryopsidophyceae        |                            |                       |                                          |                                       |
|                         | Orden: Bryopsidales            |                            |                       |                                          |                                       |
|                         | Family: Caulerpaceae           |                            |                       |                                          |                                       |
| *Codium fragile*        | Phylum: Chlorophyta            | North of the Pacific Ocean and coast of Japan | All Spain             | Widespread in the Mediterranean          | - Human consumption                   |
|                         | Class: Chlorophyceae           |                            |                       |                                          |                                       |
|                         | Orden: Codiales                |                            |                       |                                          |                                       |
|                         | Family: Codiaceae              |                            |                       |                                          |                                       |
| *Caulerpa racemosa*     | Phylum: Chlorophyta            | Tropical areas             | Except Canarias       | Mediterranean: from Spain to Turkey      | - Human consumption                   |
|                         | Class: Bryopsidophyceae        |                            |                       |                                          |                                       |
|                         | Orden: Bryopsidales            |                            |                       |                                          |                                       |
|                         | Family: Caulerpaceae           |                            |                       |                                          |                                       |
| **Diatoms**             |                               |                            |                       |                                          |                                       |
| *Didymosphenia geminata*| Phylum: Ochrophyta             | Boreal and alpine regions of North America and Northern Europe | All Spain             | New Zealand and Patagonia, South America | - Ornamental                          |
|                         | Class: Bacillariophyceae       |                            |                       |                                          |                                       |
|                         | Orden: Cymbellales             |                            |                       |                                          |                                       |
|                         | Family: Gomphonematace         |                            |                       |                                          |                                       |

The use of some algae (e.g., *Caulerpa racemosa*) as ornamental species in aquariums has also contributed to their proliferation [59,60]. Among these species, only five are considered invasive (*) or potentially invasive (**) in Galicia (northwest Spain): *Asparagopsis armata***, *Codium fragile* subs. *tomentosoides*, *Grateloupia turuturu***, *Sargassum muticum***, and *Gracilaria vermiculophylla*. Galician waters also feature the presence of two other exotic invasive species, though they do not appear in the regulation of Real Decreto (RD) 1628/201; these are *Gymnodinium catenatum* and *Bonamia ostreae* [61].

For many years, non-native species of algae have been considered threats, thus a series of methods to eradicate them from non-endemic areas have been developed and optimized. However, the marine biomass, including invasive macroalgae, is currently the focus of several industries, such as pharmaceutical, food, cosmetic, and biotechnological industries, due to their biological activities, e.g., antioxidant, antimicrobial, anti-inflammatory, anticancer. The aim of these industries is to revalorize invasive macroalgae as a source of extracts and compounds with industrial interest [8]. Although many studies have evaluated the biological properties of various extracts of *A. armata*, *C. fragile*, *G. turuturu*, *S. muticum*, and *G. vermiculophylla*, in some cases, the bioactive compounds responsible for this activity have not yet been identified. In the following paragraphs, the current knowledge about target compounds for industrial applications and the bioactive compounds identified in the
macrolaegae species considered invasive in Galicia are compiled. They are also summarized in Table 3.

3.1. Polysaccharides

In the case of *A. armata*, the polysaccharides derived from sulfated galactans have shown strong antiviral effects against human immunodeficiency virus (HIV), inhibiting its reproduction [62]. A study confirmed the inhibition of herpes simplex virus type 1 by different extracts of numerous red algae, including *A. armata*. Although the authors did not identify the compounds involved in the activity, the good results of the water extract were attributed to water-soluble polysaccharides [63]. Mannitol has been also identified in the ethanolic extract of *A. armata*, in a concentration of 34.70 mg/100 g of dry macroalgae [64].

In the case of *C. fragile*, several bioactivities have been attributed to its sulfated polysaccharides (SPs). The administration of this type of compounds reduced the oxidative damage associated with diabetes mellitus and obesity in several animal models without any cytotoxic effect [65,66]. Recently, a study stated that SPs from *C. fragile* scavenge effectively freed radicals in vitro and suppressed the oxidative damage caused by H₂O₂ in Vero cell cultures and in zebrafish [67]. It has also been reported that SPs from *C. fragile* increased the coagulation time of human blood in a dose-dependent manner according to the methods activated partial thromboplastin time (APTT) [68,69], thrombin time (TT), and prothrombin time (PT) [69]. SPs from *C. fragile* inhibited HeLa cells proliferation [70] by stimulating tumor necrosis factor (TNF)-related apoptosis-inducing ligand, a promising anticancer target [71].

**Table 3.** Main compounds and bioactive compounds reported for the invasive macroalgae in northwest Spain.

| Bioactive Compounds | Invasive Macroalgae |
|---------------------|---------------------|
| **Asparagopsis armata** | **Codium fragile** | **Gracilaria vermiculophylla** | **Sargassum muticum** | **Grateloupia turuturu** |
| Polysaccharides | Sulphated galactan derivatives, Mannitol | Sulphated polysaccharides | Fucoidans, Alginates, Glucuronic acid, Mannuronic acid, Laminarin |
| Lipids | Cholestanol, Cholesta-5,25-diene-3,24-diol, Palmitic acid, Stearic acid | Clerosterol | Cholesterol, 1-tetradecanol, 1-hexadecanol, 1-octadecanol, 1-eicosanol, 1-docosanol, Sterols, Monoacylglycerol | α-Linolenic acid |
| Proteins | | | | Phospholipids, Glycolipids, Eicosapentaenoic acid |
| Pigments | β-carotene, Siphonaxanthin | | Fucoxanthin | R-phycoerythrin |
| Vitamins | α, β, γ, δ-tocopherol, γ-tocotrienol | α-tocopherol | α, γ-tocopherol | α-tocopherol, Phytanadione (vitamin K1) |
### Bioactive Compounds

|                  | Asparagopsis armata | Codium fragile | Gracilaria vermiculophylla | Sargassum muticum | Grateloupia turuturu |
|------------------|---------------------|----------------|-----------------------------|------------------|---------------------|
| **Phenolic**     | Not specified       | Flavonoids, tannins | Gallic acid, Protocatechuic acid, Gentisic acid, Hydroxybenzoic acid, α-Vinillic acid, Syringic acid | Hydroxybenzoic acid, Gallic acid, Vanillic acid, Protocatechuic acid, Caffeic acid, Syringic acid, Chlorogenic acid, Coumaric acid, Phlorotannins, Fuhalols, Phloretols, Monofuhalol A, |                                    |
| **Other**        | Halogenated compounds, *Halogenated ketones*, 1,1-dibromo-3-iodo-2-propanone, 1,3-dibromo-2-propanone, 1,3-dibromo-1-chloro-2-propanone (**±** form), *Halogenated carboxylic acids*, Di bromoacetic acid, Bromochloroacetic acid, Dibromoacrylic acid, *Halogenated alkanes*, Bromoform, Dibromochloromethane | Serine protease | Long chain aliphatic alcohols | Tetrapernylalcohol monoterpenoid with a chrome moiety | Squalene |
| **Reference**    | [72–74]             | [75,76]        | [77]                        | [78]             | [79,80]             |

Finally, these compounds also show immune-stimulating properties in both in vitro and in vivo models. Sulfated galactan obtained from *C. fragile* stimulated murine macrophages RAW264.7 cell line, increasing the levels of nitric oxide and both pro-inflammatory and anti-inflammatory cytokines, which are fundamental for the host immune response [81–83]. In head kidney cells, SPs had a stimulatory effect on immune genes, including interleukin (IL)-1β, IL-8, TNF-α, interferon (IFN)-γ, and lysozyme [84]. Immuno-stimulant properties have been also observed in human peripheral blood dendritic cells and T cells, which were activated by SPs. This suggests that these compounds could be candidates for products aimed to enhance human immune system [85].

*S. muticum* is a source of several valuable polysaccharides, such as fucoidans, alginate, guluronic and mannuronic acids, laminarin, and their derivatives [86]. Alginate obtained from *S. muticum* has been demonstrated to possess anticancer properties, stimulating cell death in A549 cells (epithelial lung adenocarcinoma), PSN1 cells (pancreatic adenocarcinoma), HCT-116 cells (colon carcinoma), and T98G cells (glioblastoma) [87].

Finally, *G. vermiculophylla* and *G. turuturu* are being used in the phycocolloid industry for obtaining agar and carrageenan, respectively, turning them into valuable matrices [88,89]. Recently, polysaccharide extracts from *G. turuturu* have shown antimicrobial properties against *Escherichia coli* and *Staphylococcus aureus* [90].
3.2. Lipids

Starting with *A. armata*, it has been reported that these macroalgae contain some sterols such as cholesta-5,25-diene-3,24-diol, (3β,24S)-form [91], palmitic and stearic fatty acids, and cholesterol [64]. Recently, different crude extracts and fractions of this species were demonstrated to present antibacterial and antifouling properties. In the crude extract and most active fractions, several compounds were identified, including hexadecanoic, dodecanoic, octadecanoic, and tetradecanoic acids, which may be involved in this activity [92,93].

Regarding *C. fragile*, clerosterol (a derivative of cholesterol) was found in several extracts. This compound shows antioxidant properties, since it attenuated UVB-induced oxidative damage in human immortalized keratinocyte HaCaT cells and BALB/c mice models, reducing lipid and protein oxidation [94]. In addition, clerosterol stimulated apoptosis in A2058 human melanoma cells [95] and modulated several apoptotic factors in human leukemia cells [96]. Recently, a study observed that *C. fragile* displayed neuroprotective effects on neuroblastoma cell line SH-SY5Y. In the most bioactive fractions, several lipid compounds, among others, were identified. Although more research is needed, the authors considered that lipids are involved in the neuroprotective effect [97].

*G. vermiculophylla* contains high quantity of cholesterol (473.2 mg/kg dry weight), cholesterol derivatives, long-chain aliphatic alcohols, and monoglycerides, including 1-tetradecanol, 1-hexadecanol, 1-octadecanol, 1-eicosanol, and 1-docosanol [77]. Other lipids of great interest for nutraceutical and biotechnological industries include phospholipids, glycolipids, and eicosapentaenoic acid, present in high levels in this alga [79]. For example, three sphingolipids (gracilarioside, and gracilamides A and B) isolated from *G. vermiculophylla* (accepted name of *G. asiatica*) showed moderate cytotoxic effects against human A375-S2 melanoma cell line [98].

3.3. Proteins

To our knowledge, only *G. vermiculophylla* presents bioactive compounds of protein nature. This alga can absorb UV-A and UV-B radiations and decrease free radicals-induced effects, resulting from its high content in mycosporine-like amino acids [99].

3.4. Pigments

Siphonaxanthin from *C. fragile* has shown anticancer properties, stimulating the apoptosis of A549 lung cancer cells and modulating apoptotic factors in human leukemia cells [95,96]. Moreover, the anti-angiogenic effect of siphonaxanthin has been described in human umbilical vein endothelial cells as well as in a rat aortic ring angiogenic model [100], which suggests that this biomolecule could be an alternative to prevent pro-angiogenic diseases such as cancer. In addition, this alga also contains β-carotene [76].

In recent years, fucoxanthin has received a great deal of interest from the scientific community and industry due to the many beneficial health properties attributed to it, including anti-inflammatory [101]. Fucoxanthin extracted from *S. muticum* inhibited the lipopolysaccharide-induced nitric oxide production in RAW 264.7 macrophages and inhibited the expression of pro-inflammatory cytokines [102,103].

At industrial scale, *G. turuturu* is also used to produce R-phycoerythrin, a pink-purple pigment soluble in water present in large quantities, which presents diverse biological properties and potential industrial applications [89,104].

3.5. Vitamins

Different vitamins have been identified in the selected macroalgae, except in *A. armata*. In *C. fragile*, high levels of tocopherols have been reported (1617.6 µg/g lipid), including α, β, γ, and δ tocopherol and γ-tocotrienol [76]. *G. vermiculophylla* showed a considerable α-tocopherol content (28.4 µg/g of extract) [105]. Regarding *G. turuturu*, a chemical analysis revealed the presence of α-tocopherol and phytonadione (vitamin K1) [80]. Finally,
S. muticum contains high amounts of α- and γ-tocopherol, 218 and 20.8 µg/g of extract, respectively [105].

3.6. Phenolic Compounds

Phenolic content has been evaluated in several species, although not all the studies have identified the target compounds. In the case of A. armata, phenolic content was determined by the Folin–Ciocalteu spectrophotometry method, which showed that it represented 1.13 ± 0.05% of dry weight [106]. Different extracts of C. fragile also contain phenolic compounds, mainly flavonoids and, to a lesser extent, tannins. These compounds showed a correlation with the antioxidant activity of the macroalgae [75]. The previous study of Farvin and Jacobsen (2013) identified several phenolic acids in both G. verniculophylla aqueous extracts (gallic, protocatechuic, hydroxybenzoic, vanillic, syringic, and salicylic acids) and ethanolic extracts (gallic, protocatechuic, and gentisic acids). In correspondence with its content in phenolic compounds, a high antioxidant capacity has been demonstrated for these macroalgae according to the 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and the ferric antioxidant power (FRAP) methods. In addition, G. verniculophylla extracts inhibited lipid peroxidation [105]. Finally, some authors have reported the presence of phenolic compounds in S. muticum, including (ordered from highest to lowest concentration): hydroxybenzoic and gallic acids, p-hydroxybenzaldehyde, vanillic acid, 3,4-dihydroxybenzaldehyde and protocatechuic, ferulic, p-coumaric, caffeic, syringic, and chlorogenic acids [107]. Several bioactivities of S. muticum, such as antioxidant, antimicrobial, anticancer, or anti-inflammatory, have been attributed to the presence of phenolic compounds with high antioxidant capacity, particularly to phlorotannins (e.g., phloroglucinol, diphlorethol, bifuhalol), which are exclusively found in marine seaweed [78,108–111].

3.7. Other Minor Compounds

The invasive species A. armata presents high levels of halogenated secondary metabolites with recognized antibiotic activity [112]. They act as chemical defense against grazers and epibiota [113] and may be suitable for a wide range of applications [114,115]. For instance, the major metabolites bromoform and dibromoacetic acid, along with dibromochloromethane, bromochloroacetic acid, and dibromoacrylic acid, have shown high antifouling potential [72–74]. They can decrease the density of six bacteria strains on the algae surface: two marine (Vibrio harveyii and V. alginolyticus) and four biomedical strains (Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermis, and Escherichia coli) [116]. Recently, several brominated compounds, such as tribromomethanol, were found in the crude extract and fractions of A. armata, which showed antimicrobial antifouling potential [92,93].

A serine protease extracted from C. fragile was demonstrated to exert in vitro and in vivo anticoagulant and fibrinogenolytic activity [117]. Finally, it was found that G. turuturu contains squalene, which was reported to exert several beneficial activities [80].

4. Current Strategies to Obtain Bioactive Compounds from Algae

Algae have been considered as potential sources for the extraction of bioactive compounds with applications in food, cosmetic, pharmaceutical, or other industrial sectors. However, one of the most limiting steps when referring to obtaining bioactive compounds from natural sources is the extraction system, and, thus, upscale and downstream processes in the case of its industrial application [118]. Table 4 summarizes some examples of extraction techniques applied for the recovery of bioactive compounds from the studied invasive species.

For the final purpose of extracting bioactive compounds, several techniques of pretreatments and extraction have been thoroughly described. Traditionally, pretreatments consist of using hot air drying, chemical treatments with acids, salts, or surfactants. Nevertheless, novel extraction techniques (explained below) have also been successfully applied as pretreatments for algae [119].
4.1. Conventional Extraction Techniques

Conventional extraction techniques were deeply investigated during the past decades for their easiness of application and low requirements, but, also for this reason, they continue to be the most used [120]. As it can be seen in Table 4, the techniques that have been more frequently applied are maceration, Soxhlet, and heat assisted extraction (HAE). These methodologies are applied using different solvents, heat, and/or stirring in some cases. Moreover, in the case of Soxhlet extraction, the recircularization of the solvent during longer time periods is aimed at improving the extraction yield [121]. Additionally, heat favors the mass transfer of the bioactive compounds to the solvent through the disruption of cell walls [122].

Table 4. Extraction techniques for obtaining bioactive compounds from the invasive macroalgae in northwest Spain.

| Method   | Conditions                        | Compounds                          | Activities                              | Model/Assay                                                                 |
|----------|-----------------------------------|------------------------------------|-----------------------------------------|----------------------------------------------------------------------------|
| **Asparagopsis armata** | | | | |
| Soxhlet  | Chloroform-methanol (3:2), dichloromethane (100%), methanol (100%), and water (100%), 8 h | - | Anti-Herpes Simplex Virus and cytotoxicity   | Neutral red dye method on Vero cells. [63] |
| Mac     | Hexane, dichloromethane, and ethanol | Halogenated compounds               | Antiprotozoal                           | Leishmania donovani promastigotes cultures [123] |
| Mac     | 0.025 g/mL; methanol, 16 h, 20 °C | Phenolic compounds                  | Antioxidant and neuroprotective         | DPPH, CCA, ICA, AChe, BuChE, TYRO inhibition. In vivo MTT assay on SH-SY5Y cells on H2O2 induced cytotoxicity. [124] |
| HAE     | 0.04 g/mL; distilled water, 5 h, 96 °C | Polysaccharides                     | Anti-HIV                                | Human immunodeficiency virus (HIV) induced syncytium formation on MT4 cells. [62] |
| PLE     | Dichloromethane methanol (1:1; v:v), 75 °C, 1500 psi, 7 min (×2) | Phenolic compounds                  | Antioxidant and cytotoxicity           | Radical-scavenging activity (DPPH). Reducing activity. Daudi, Jurkat and K562 cell lines. [106] |
| **Codium fragile** | | | | |
| Mac     | 80% methanol (×3), Butanol and ethyl-acetate fractions. | Clerosterol                         | Antioxidant and anti-inflammatory      | In vivo MTT assay on human keratinocyte HaCaT cells irradiated with UVB and BALB/c mice models. Expression of pro-inflammatory proteins and mediators. [94] |
| Mac     | Hexane, ethyl, and methanol (×3) | -                                  | Antioxidant and anti-hypertensive      | DPPH and ABTS inhibition In vitro ACE inhibitory assay [75] |
| Mac     | 80% methanol                     | -                                  | Anti-inflammatory                      | Lipopolysaccharide-stimulated RAW 264.7 [125] |
| Mac     | 80% methanol                     | -                                  | Anti-cancer                            | Human breast cancer cell line MDA-MB-231 [126] |
| HAE     | 0.02 g/mL; water, 12 h, 60 °C | Polysaccharides                     | Anticoagulant                          | APTT assay on human blood [68] |
| HAE     | 10 vol, distilled water, 1 h, 95 °C | -                                  | Anti-inflammatory and anti-edema       | LPS-stimulated RAW 264.7 and carrageenan-induced paw edema in male Sprague-Dawley rats. [127] |
| HAE     | Ethanol 96% (v/v), 3 h, 70 °C (×3) | -                                  | Anti-inflammatory                      | LPS-stimulated RAW 264.7. [128] |
| HAE     | Distilled water, 4 h, 90 °C. | -                                  | Anti-inflammatory, alleviation of cartilage destruction | Primary chondrocytes cells, osteoarthritis rat model. [129] |
| **Gracilaria vermiculophylla** | | | | |
| Mac     | 0.1 g/mL; water or ethanol, 96%, 12 h, room temperature. | Phenolic compounds                  | Antioxidant                             | In vitro assays (DPPH, FRAP, ferrous ion-chelating) and liposome model system. [105] |
| Soxhlet | 0.3 g/mL; ethyl acetate; 72 h. | -                                  | Antimicrobial                          | Strains of S. enteritidis, P. Aeruginosa and L. innocua [121] |
### Table 4. Cont.

| Method | Conditions | Compounds | Activities | Model/Assay | Ref. |
|--------|------------|-----------|------------|-------------|-----|
| S/L    | 1/20 ratio (w/v), water, 20 min, phosphate buffer (20 mM, pH 7.1) | - | Antibacterial | European abalone pathogen Vibrio harveyi | [130] |
| Sargassum muticum | | | | | |
| Mac    | 0.01 g/mL; 80% methanol, 24 h, RT. | Fucoxanthin | Anti-inflammatory | LPS-stimulated RAW 264.7 macrophages | [103] |
| Mac    | 0.1 g/mL; Water or ethanol, 96%, 12 h, RT. | Phenolic compounds | Antioxidant | In vitro assays (DPPH, FRAP, ferrous ion-chelating) and liposome model system | [105] |
| Mac    | Dichloromethane or methanol, 1:4 (w/v), 12 h. | Phenolic compounds | Antioxidant and cytoprotective effect | In vitro assays (DPPH and ORAC) Protective effect on MCF-7 cells | [131] |
| HAE    | Methanol:water (1:10), 3 h, 65 °C (×3) | Chromane meroterpenoid | Photodamage attenuation | Human dermal fibroblasts | [132] |
| SFE    | CO₂, 10% ethanol, 15.2 MPa, 60 °C, 90 min (static) | - | Antioxidant | Not reported | [133] |
| PLE    | Ethanol:water (95:5); 160 °C, 10.3 MPa, 20 min (×2) | Phlorotannins | Antiproliferative | HT-29 adenocarcinoma colon cancer cells | [134] |
| UAE    | Water at S/L ratio of 1:20; 5–30 min, RT (25 °C), 5 A, 150 W and 40 Hz. | Alginate | Cytotoxic effect | A549, HCT-116, PSN1, and T98G cells | [87] |
| Autohydrolysis | 96% ethanol | - | Antioxidant, anti-inflammatory and anti-irritant | In vitro assays (FRAP, DPPH and ABTS). Reconstructed human epidermis test method. Irritability assays with the EpiSkin test. | [108] |
| Autohydrolysis | RT, formaldehyde 1% (15 h), sulfuric acid 0.2 N (4 h), and sodium carbonate 1% (15 h). | Phlorotannins | Anti-tumor and anti-inflammatory | A549, HCT-116, PSN1, and T98G cells. Neutrophils’ oxidative burst oxidation of luminol. | [78] |

Extraction method: PLE: pressurized liquid extraction; S/L: solid–liquid; SFE: supercritical fluid extraction; UAE: ultrasound assisted extraction; Mac: maceration; RT: room temperature. Assays: DPPH: 1,1-Diphenyl-2-picrylhydrazyl; ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; CCA: copper chelating activity; ICA: iron chelating activity; AChE: acetylcholinesterase; BuChE: butyrylcholinesterase; TYRO: tyrosinase; ACE: angiotensin converting enzyme; APTT: activated partial thromboplastin Time; ORAC: oxygen radical absorbent capacity; FRAP: ferric antioxidant power. Cell lines: Vero: African green monkey kidney cell line; MT4: leukemia cell line; HaCaT: aneuploid immortal keratinocyte cell line; RAW 264.7: murine macrophage cell line; MCF-7: human breast cancer cell line; A549: adenocarcinomic human alveolar basal epithelial cells; HCT-116: human colon cancer cell line; PSN1: human pancreatic cancer cell line; T98G: glioblastoma cell line.

#### 4.2. Novel Extraction Techniques

On the other hand, emerging or novel techniques are also increasing as new methods directed towards a more sustainable process, with lower times and energy consumption or higher yields. Among them, some examples must be highlighted: microwave assisted extraction (MAE), ultrasounds assisted extraction (UAE), pressurized liquid assisted extraction (PLE), enzyme assisted extraction (EAE), high pressure assisted extraction (HPAE), pulsed electric field (PEF), supercritical fluid extraction (SFE), and hydrothermal liquefaction. At last, new options are being explored that combine approaches of different techniques [119]. Table 4 shows some of the examples when these techniques have been applied on invasive species.

Considering the information collected, obtaining processes of bioactive compounds from these invasive species utilizes a wide range of conventional and novel sample preparation and extraction techniques. Once the extraction has been performed, it is necessary to characterize and quantify the compounds present in the extract. To carry out this process, the most used techniques are based on chromatographic methods [135]. These methods are regularly evolving and currently coupled to different detectors. Nuclear magnetic resonance, mass spectrometry, vibrational spectrometry, or a combination of several tech-
techniques are some of the approaches currently applied. All of them are focused on separating, detecting, characterizing, and quantifying those bioactive molecules as well as elucidating their structures and their function on the metabolic pathways they are involved in [136].

5. Algae as Supplement of Diets in Aquaculture

Aquaculture has grown very fast in the last decades, reaching expansion rates higher than other major food production sectors. By 2016, the aquaculture relevance as an animal protein source was underlined by its huge global production that reached nearly 80 million tons. Among the European countries, Spain is expected to reach more than 0.3 Mt of annual production [137]. This exponential growth has been prompted by the low feed conversion ratio that aquaculture species exhibit, 1.1–1.6 kg of feed/kg of edible fish, against livestock, which can reach maximum ratios of 9 kg of feed/kg of beef [138,139]. However, for the aquaculture sector to continue growing at a constant rate, the supply of nutrients and feed will have to grow at a similar rate [140]. Finding appropriate ingredients to substitute the limited marine resources generally used in aquaculture feeds has been challenging the sector for decades. Therefore, it is necessary to develop new and more sustainable food sources for aquaculture use. In this sector, macroalgae has been proposed as a possible protein source in the fish feed but also as a source of bioactive compounds, which may improve the nutritional values and exert beneficial effects on animal health, including antioxidant, antimicrobial, or positive effects on immune system [141]. Invasive algae may be possible candidates for these uses. This kind of exploitation will permit obtaining compounds from sustainable sources for industrial application while reducing the population of invasive species, providing double profit. However, several limitations of the use of macroalgae species in aquaculture feeds have been identified. For example, from a nutritional point of view, it would be necessary to eliminate compounds that may be anti-nutritive or to develop methods to reduce polysaccharides to increase the digestibility [142]. In addition, in some cases, knowledge gaps about the compounds involved in the observed effects and the mechanisms of action still persist. Therefore, the use of some species in aquaculture is still limited, and more research is necessary before their application.

Regarding the selected invasive algae species, different examples along the scientific literature reported their beneficial effects in the nutrition of several aquaculture animals. The use of *A. armata*, under the commercial powder presentation named after Ysaline®100, was assessed for the development of *Sparus aurata* larvae. Among the experimental parameters analyzed—growth, survival, anti-bacterial activity, microbiota quantification, digestive capacity, stress level, and non-specific immune—the last three were not affected when *A. armata*-based feed was utilized. Besides, this diet significantly reduced the amount of Vibrionaceae present in water and larval gut and enhanced growth rate. It was suggested that mortality produced when high concentrations of *A. armata*-based feed were used will improve if lower amounts are used until 10 days after hatching, promoting a safer rearing environment [143]. Recently, extracts of *A. armata* were used to supplement the fed of the whiteleg shrimp (*Penaeus vannamei*). The results showed that the formulation increased the survival rate in presence of *Vibrio parahaemolyticus* (causative agent of acute hepatopancreatic necrosis disease) and reduced the food contamination caused by fungus [144].

As previously mentioned, a recent study stated the protective effect of SPs extracted from *C. fragile* against free radicals. These molecules were demonstrated to suppress the oxidative damage induced by oxygen peroxide in the main fish live model, zebrafish. Embryos at 7–9 h post-fertilization stage were incubated with different concentrations of SPs from *C. fragile* for 1 h and then exposed to the pro-oxidant agent for another 14 h. Obtained results indicated that the pre-treatment of zebrafish with *C. fragile* SPs can protect animals against oxidative stress by reducing reactive oxygen species, minimizing cell death and lipid peroxidation. This antioxidant capacity of *C. fragile* SPs can be relevant for the development of innovative fishmeal [67]. In another study, *C. fragile* SPs exerted immuno-stimulating effects on olive flounder (*Paralichthys olivaceus*), up-regulating the
expression of interleukins 1β and 8, TNF-α, interferon-γ, and lysozyme genes, all of them involved in the immune response. Thus, this species could be used as feed additive to improve the immune system of the fish [84].

*G. vermiculophylla* has been repeatedly tested in experimental diets, especially aimed at freshwater fish species such as rainbow trout (*Oncorhynchus mykiss*). The apparent digestibility coefficient for trout of proteins and lipids from a *G. vermiculophylla* based diet was like that of the reference diets [145]. Additionally, another work in which *G. vermiculophylla* was utilized for designing experimental diets for rainbow trout demonstrated some benefits for animal health that also reflect an economical benefit for improving the quality of the finally commercialized product. The inclusion of this invasive alga in 5% doubled the flesh iodine levels, which ultimately improved the fillet color intensity and juiciness since it enhanced the carotenoid deposition, which can be also associated with a better conservation of the final product for the antioxidant properties related to carotenoid pigments [146]. In another study, the inclusion of 5% of this species in the diet of *O. mykiss* was reported to enhance the immune system of the animals by increasing lysozyme, peroxidase, and complementing system activities, which play a key role in the defense against pathogens [147]. Finally, the effect of supplementation of heat-treated *G. vermiculophylla* was evaluated in gilthead seabream (*Sparus aurata*) submitted to acute hypoxia and successive recovery. Compared to the control, the dietary inclusion of the macroalgae reduced the antioxidant stress caused by the hypoxia, and the survival rate was higher [148]. More recently, the immunomodulatory effect of *G. vermiculophylla* has been evaluated in the shrimp *Litopenaeus vannamei*. Co-culture with diverse macroalgae species (including *G. vermiculophylla*) improved the immune response of the shrimps against the pathogen *V. parahaemolyticus* and white spot virus, increasing the production of hemocytes and the activity of superoxide dismutase (SOD) and catalase (CAT) compared to control [149].

Very scarce information regarding the development of experimental diets formulated with *S. muticum* has been found. However, at least one study performed its inclusion and tested its effect in African catfish, *Clarias gariepinus*. As in previous works, they added 5% of alga and fed animals for 12 weeks. In the skin of fish fed with probiotics diet, an improved glutathione S-transferase (GST) and SOD activity and less CAT activity were recorded, whereas in the livers from fishes fed with *S. muticum*, a better oxidative status with improved GST and CAT activities were displayed. This positive effect on antioxidant enzyme activity has been suggested to ultimately improve the resistance of animals against bacterial infections [150]. Other species belonging to the *Sargassum* genus have been described as immunomodulators and growth promoters for great sturgeon (*Huso huso*) and as immunobooster for shrimp (*Fenneropenaeus chinensis*) to which they also provide specific resistance to vibriosis [151,152].

Finally, experimental diets aimed to feed cultivated hybrid abalone cross (*Haliotis rubra* and *Haliotis laevigata*) were designed using several macroalgae, i.e., *G. turuturu* together with *Ulva australis* and/or *U. lactevirens*. Treatment applied for 12 weeks period provided a significant higher growth rate of abalone in terms of length and weight. Besides, it improved abalone health and its nutritional composition, since animals showed, by the end of the assay, tissues with higher carbohydrate/protein ratio, ash content, and lower lipid amount [153]. Other studies in which *G. turuturu* mixed with *P. palmata* was used as feed for the European abalone *Haliotis tuberculate* demonstrated that the combination of algae did not produce animals’ mortality, and it improved growth rates (in length and weight) while increasing the final content of lipid in the abalone [154]. Besides, in another work, the capacity of *G. turuturu* was underlined for inhibiting, in a quantity of 16%, the growth of the main pathogen of the *H. tuberculata*, that is, *Vibrio harveyi* [130]. Therefore, the inclusion of this invasive alga in experimental diets may provide nutritional value to abalone but also antibacterial activity which ultimately reduces mortalities.
6. Future Perspectives and Conclusions

According to the compiled studies, Asparagopsis armata, Codium fragile subs. tomentosoides, Grateloupia turuturu, Sargassum muticum, and Gracilaria vermiculophylla can be considered as alternative sources of bioactive compounds which could be further used for industrial applications. Thus, revalorization strategies will make it possible to obtain new compounds from sustainable sources but also reduce the population of invasive species, generating a double benefit. Nevertheless, two key concerns limit their further use. From the scientific and the technological points of view, more research is still required to increase the profitability of the extraction process. Therefore, the applicability of different techniques needs to be further investigated to assess which is the most favorable process, comparing both conventional and modern extraction techniques. In addition, in some cases, it is still necessary to identify the specific compounds responsible for the observed activities and to determine their action mechanisms. Nevertheless, the development of invasive algae harvesting methods generates a series of drawbacks. The main one is that the revalorization of invasive algae could lead to an increase of their populations instead of eliminating them due to the economic benefits that could be obtained from their use. In fact, this economic revenue would not be difficult to achieve, since these invasive algae are often characterized by a high reproductive rate. Considering this drawback, the collection of invasive species should be subjected to a strict policy. A principle that should be considered is that the only legal collectors of invasive algae should be those companies whose activity is reduced by the presence of these organisms (e.g., shellfish catchers/farmers, inshore fishermen, diving companies, etc.). This would prevent the harvesters themselves from “planting” more invasive algae to further increase their profits.

Author Contributions: Conceptualization, M.A.P. and J.S.-G.; methodology, A.G.P., C.L.-L., M.C., M.F.-C., P.G.-O.; formal analysis, A.G.P., C.L.-L., M.C., M.F.-C., P.G.-O.; investigation, A.G.P., C.L.-L., M.C., M.F.-C., P.G.-O.; writing—original draft preparation, A.G.P., C.L.-L., M.C., M.F.-C., P.G.-O.; writing—review and editing, M.A.P. and J.S.-G.; supervision, M.A.P. and J.S.-G.; project administration, M.A.P. and J.S.-G. All authors have read and agreed to the published version of the manuscript.

Funding: The research leading to these results was funded by Xunta de Galicia supporting the Axudas Conecta Peme, the IN852A 2018/58 NeuroFood Project, and the program EXCELENCIA-ED431F 2020/12; to Ibero-American Program on Science and Technology (CYTED—AQUA-CIBUS, P317RT0003) and to the Bio Based Industries Joint Undertaking (JU) under grant agreement No 888003 UP4HEALTH Project (H2020-BBI-JTI-2019). The JU receives support from the European Union’s Horizon 2020 research and innovation program and the Bio Based Industries Consortium. The project SYSTEMIC Knowledge hub on Nutrition and Food Security has received funding from national research funding parties in Belgium (FWO), France (INRA), Germany (BLE), Italy (MIPAAF), Latvia (IZM), Norway (RCN), Portugal (FCT), and Spain (AEI) in a joint action of JPI HDHL, JPI-OCEANS, and FACCE-JPI launched in 2019 under the ERA-NET ERA-HDL (n° 696295).

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The research leading to these results was supported by MICINN supporting the Ramón y Cajal grant for M.A. Prieto (Ryc-2017-22891); by Xunta de Galicia for supporting the postdoctoral grant of M. Fraga-Corral (ED481B-2019/096), the pre-doctoral grants of P. García-Oliveira (ED481A-2019/ 295) and Antía González Pereira (ED481A-2019/0228); by University of Vigo for the predoctoral grant of M. Carpena (Uvigo-00VI 131H 6410211) and by UP4HEALTH Project that supports the work of C. Lourenço-Lopes.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Máximo, P.; Ferreira, L.M.; Branco, P.; Lima, P.; Lourenço, A. Secondary metabolites and biological activity of invasive macroalgae of southern Europe. Mar. Drugs 2018, 16, 265. [CrossRef]
2. Shackleton, R.T.; Shackleton, C.M.; Kull, C.A. The role of invasive alien species in shaping local livelihoods and human well-being: A review. J. Environ. Manag. 2019, 229, 145–157. [CrossRef]
3. Pyšek, P.; Hulme, P.E.; Simberloff, D.; Bacher, S.; Blackburn, T.M.; Carlton, J.T.; Dawson, W.; Essl, F.; Foxcroft, L.C.; Genovesi, P.; et al. Scientists’ warning on invasive alien species. *Biol. Rev.* **2020**, *95*, 1511–1534. [CrossRef] [PubMed]

4. Otero, M.; Cebrian, E.; Francour, P.; Galil, B.; Savini, D. Monitoring Marine Invasive Species Areas (MPAs)—A Strategy and Practical Guide for Managers; IUCN: Malaga, Spain, 2013.

5. Commission European. *Invasive Alien Species of Union Concern*; Commission European: Luxembourg, 2020.

6. Milledge, J.J.; Nielsen, B.V.; Bailey, D. High-value products from macroalgae: The potential uses of the invasive brown seaweed, Sargassum muticum. *Rev. Environ. Sci. Biotechnol.* **2015**, *14*, 67–88. [CrossRef]

7. Davout, D.; Surgut, G.; Stiger-Pouvreau, V.; Noisette, F.; Riera, P.; Stagnol, D.; Androuin, T.; Poupart, N. Multiple effects of a Gracilaria vermiculophylla strain on estuarine mudflat functioning and diversity. *Mar. Environ. Res.* **2017**, *131*, 227–235. [CrossRef]

8. Pinteus, S.; Lemos, M.F.L.; Alves, C.; Neugebauer, A.; Silva, J.; Thomas, O.P.; Botana, L.M.; Gaspar, H.; Pedroza, R. Marine invasive macroalgae: Turning a real threat into a major opportunity—the biotechnological potential of *Sargassum muticum* and *Asparagopsis armata*. *Algal Res.* **2018**, *34*, 217–234. [CrossRef]

9. Machmudah, S.; Diono, W.; Kanda, H.; Goto, M. Supercritical fluids extraction of valuable compounds from algae: Future perspectives and challenges. *Eng. J.* **2018**, *22*, 13–30. [CrossRef]

10. Buschmann, A.H.; Camus, C.; Infante, J.; Neori, A.; Israel, A.; Hernández-González, M.C.; Pereda, S.V.; Gomez-Pinchetti, J.L.; Golberg, A.; Tadmor-Shalev, N.; et al. Seaweed production: Overview of the global state of exploitation, farming and emerging research activity. *Eur. J. Phycol.* **2017**, *52*, 391–406. [CrossRef]

11. Fernández-Segovia, I.; Lerma-García, M.J.; Fuentes, A.; Barat, J.M. Characterization of Spanish powdered seaweeds: Composition, antioxidant capacity and technological properties. *Food Res. Int.* **2018**, *111*, 212–219. [CrossRef] [PubMed]

12. Gómez-Zavaglia, A.; Prieto Lage, M.A.; Jiménez-López, C.; Mejuto, J.C.; Simal-Gándara, J. The Potential of Seaweeds as a Source of Functional Ingredients of Prebiotic and Antioxidant Value. *Antioxidants* **2019**, *8*, 406. [CrossRef]

13. Gomez, L.P.; Alvizure, C.; Zhao, M.; Tiwari, U.; Curtin, J.; Garcia-Vaquero, M.; Tiwari, B.K. Innovative processing strategies and technologies to obtain hydrocolloids from macroalgae for food applications. *Carbohydr. Polym.* **2020**, *248*, 116784. [CrossRef]

14. Camacho, F.; Macedo, A.; Malcata, F. Potential industrial applications and commercialization of microalgae in the functional food and feed industries: A short review. *Mar. Drugs* **2019**, *17*, 312. [CrossRef]

15. Matos, Á.P. The Impact of Microalgae in Food Science and Technology. *JAOCS J. Am. Oil Chem. Soc.* **2017**, *94*, 1333–1350. [CrossRef]

16. Soleymani, M.; Rosentramer, K.A. Techno-economic analysis of biofuel production from macroalgae (Seaweed). *Bioengineering* **2017**, *4*, 92. [CrossRef] [PubMed]

17. Culaba, A.B.; Ubando, A.T.; Ching, P.M.L.; Chen, W.H.; Chang, J.S. Biofuel from microalgae: Sustainable pathways. *Sustainability* **2020**, *12*, 9. [CrossRef]

18. Milano, J.; Ong, H.C.; Masjuki, H.H.; Chong, W.T.; Lam, M.K.; Loh, P.K.; Vellayan, V. Microalgae biofuels as an alternative to fossil fuel for power generation. *Renew. Sustain. Energy Rev.* **2016**, *58*, 180–197. [CrossRef]

19. Shuba, E.S.; Kifle, D. Microalgae to biofuels: ‘Promising’ alternative and renewable energy, review. *Renew. Sustain. Energy Rev.* **2018**, *81*, 743–755. [CrossRef]

20. Blunt, J.W.; Carroll, A.R.; Copp, B.R.; Davis, R.A.; Keyzers, R.A.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2018**, *35*, 8–53. [CrossRef] [PubMed]

21. Holdt, S.L.; Kraan, S. Bioactive compounds in seaweed: Functional food applications and legislation. *J. Appl. Phycol.* **2011**, *23*, 543–597. [CrossRef]

22. Silva, A.; Silva, S.A.; Carpena, M.; García-Oliveira, P.; Gullón, P.; Barroso, M.F.; Prieto, M.A.; Simal-Gándara, J. Macroalgae as a source of valuable antimicrobial compounds: Extraction and applications. *Antibiotics* **2020**, *9*, 642. [CrossRef]

23. Gopeechund, A.; Bhagooli, R.; Neergheen, V.S.; Bolton, J.J.; Foxcroft, L.C.; Genovesi, P.; et al. Scientists’ warning on invasive alien species. *Biol. Rev.* **2020**, *95*, 1511–1534. [CrossRef] [PubMed]

24. Bedoux, G.; Hardouin, K.; Burel, A.S.; Bourgougnon, N. Bioactive components from seaweeds: Cosmopolitan applications and future development. In *Advances in Botanical Research*; Academic Press: Cambridge, MA, USA, 2020; pp. 257–275. ISBN 9780128195413.

25. Cikoš, A.-M.; Jerković, I.; Molnar, M.; Šubarić, D.; Jokić, S. New trends for macroalgal natural products applications. *Nat. Prod. Res.* **2019**, 1–12. [CrossRef]

26. Kim, S.K. Marine Cosmeceuticals: Trends and Prospects, 1st ed.; Kim, S.K., Ed.; Tayor & Francis Group: Boca Ratón, FL, USA, 2012; ISBN 9781439860281.

27. Bedoux, G.; Hardouin, K.; Burel, A.S.; Bourgougnon, N. Bioactive components from seaweeds: Cosmopolitan applications and future development. In *Advances in Botanical Research*; Academic Press: Cambridge, MA, USA, 2014.

28. Verdy, C.; Branka, J.-E.; Mekideche, N. Quantitative assessment of lactate and progermin production in normal human cutaneous cells during normal ageing: Effect of an Alaria esculenta extract. *Int. J. Cosmet. Sci.* **2011**, *33*, 462–466. [CrossRef]

29. Nizard, C.; Friguet, B.; Moreau, M.; Bulteau, A.-L.; Saunois, A. Use of Phaeodactylum Algae Extract as Cosmetic Agent Promoting the Proteasome Activity of Skin Cells and Cosmetic Composition Comprising Same. U.S. Patent 7,220,417, 22 May 2007.

30. Hwang, E.; Park, S.Y.; Sun, Z.; Shin, H.S.; Lee, D.G.; Yi, T.H. The Protective Effects of Fucosterol Against Skin Damage in UVB-Irradiated Human Dermal Fibroblasts. *Mar. Biotechnol.* **2014**, *16*, 361–370. [CrossRef] [PubMed]
55. Boletín Oficial del Estado. Real Decreto 630/2013, de 2 de Agosto, por el que se Regula el Catálogo Español de Especies Exóticas Invasoras; Boletín Oficial del Estado: Madrid, Spain, 2013.

56. Mulas, M.; Bertocci, I. Devil’s tongue weed (Grateloupia turuturu Yamada) in northern Portugal: Passenger or driver of change in native biodiversity? Mar. Environ. Res. 2016, 118, 1–9. [CrossRef]

57. Altamirano, M.; Muñoz, A.R.; de la Rosa, J.; Barrajón-Mínguez, A.; Barrajón-Domenech, A.; Moreno-Robledo, C.; del Arroyo, M.C. The invasive species Asparagopsis taxiformis (Bonnemaisoniales, Rhodophyta) on andalusian coasts (Southern Spain): Reproductive stages, new records and invaded communities. Acta Botánica Malacit. 2008, 23, 5–15. [CrossRef]

58. Bellísimo, G.; Galfo, F.; Nicastro, A.; Costantini, R.; Castriota, L. First record of the invasive green alga Codium fragile ssp. fragile (Chlorophyta, Bryopsidales) in Abruzzi waters, central Adriatic sea. Acta Alim. Adriat. 2018, 59, 207–212. [CrossRef]

59. Gennaro, P.; Piauzzi, L. The indirect role of nutrients in enhancing the invasion of Caulerpa racemosa var. cylindracea. Biol. Invasions 2014, 16, 1709–1717. [CrossRef]

60. Ornano, L.; Sanna, C.; Serafini, M.; Bianco, A.; Donno, Y.; Ballero, M. Phytochemical study of Caulerpa racemosa (Forsk.) J. Agarth, an invading alga in the habitat of La Maddalena Archipelago. Nat. Prod. Res. 2014, 28, 1795–1799. [CrossRef]

61. Capdevila-Argüelles, L.; Zilletti, B.; Gennaro, P.; Piazzi, L. The indirect role of nutrients in enhancing the invasion of Caulerpa racemosa var. cylindracea. Biol. Invasions 2014, 16, 1709–1717. [CrossRef]

62. Haslin, C.; Lahaye, M.; Pellegrini, M.; Chermann, J.C. In Vitro Anti-HIV Activity of Sulfated Cell-Wall Polysaccharides from Gracilaria chilensis and Porphyra yezoensis. Food Chem. 2013, 138, 1819–1828. [CrossRef]

63. Kolsi, R.B.A.; Jardak, N.; Hajkacem, F.; Chaaben, R.; Jribi, I.; El Feki, L.; Belghith, H.; et al. Anti-obesity effect and protection of liver-kidney functions by Codium fragile sulphated polysaccharide on high fat diet induced obese rats. Int. J. Biol. Macromol. 2018, 117, 407–417. [CrossRef]

64. Kolsi, R.B.A.; Jardak, N.; Hajkacem, F.; Chaaben, R.; Jribi, I.; El Feki, A.; Rebai, T.; Jamoussi, K.; Fki, L.; Belghith, H.; et al. Antioxidant and antihypertensive properties of green alga (Codium fragile) from the coast of Sfax. J. Pharmacogn. Phytochem. 2018, 9, 101891. [CrossRef] [PubMed]

65. Kolsi, R.B.A.; Jardak, N.; Hajkacem, F.; Chaaben, R.; Jribi, I.; El Feki, A.; Rebai, T.; Jamoussi, K.; Fki, L.; Belghith, H.; et al. Antioxidant and antihypertensive properties of green alga (Codium fragile) from the coast of Sfax. J. Pharmacogn. Phytochem. 2018, 9, 101891. [CrossRef] [PubMed]

66. Kolsi, R.B.A.; Jardak, N.; Hajkacem, F.; Chaaben, R.; Jribi, I.; El Feki, L.; Belghith, H.; et al. Antioxidant and antihypertensive properties of green alga (Codium fragile) from the coast of Sfax. J. Pharmacogn. Phytochem. 2018, 9, 101891. [CrossRef] [PubMed]

67. Kolsi, R.B.A.; Jardak, N.; Hajkacem, F.; Chaaben, R.; Jribi, I.; El Feki, L.; Belghith, H.; et al. Antioxidant and antihypertensive properties of green alga (Codium fragile) from the coast of Sfax. J. Pharmacogn. Phytochem. 2018, 9, 101891. [CrossRef] [PubMed]

68. Athukorala, Y.; Lee, K.W.; Kim, S.K.; Jeon, Y.J. Anticoagulant activity of marine green and brown algae collected from Jeju Island in Korea. Bioresour. Technol. 2013, 148, 367–374. [CrossRef]

69. Ciancia, M.; Quintana, I.; Vizcarrédez-Larráyoz, A.; Barrajón-Mínguez, A.; Barrajón-Domenech, A.; Moreno-Robledo, C.; del Arroyo, M.C. The invasive species Asparagopsis armata (Bonnemaisoniales, Rhodophyta) on andalusian coasts (Southern Spain): Reproductive stages, new records and invaded communities. Acta Botánica Malacit. 2008, 23, 5–15. [CrossRef]

70. Surayot, U.; You, S.G. Structural effects of sulfated polysaccharides from Codium fragile on NK cell activation and cytotoxicity. Int. J. Biol. Macromol. 2017, 98, 117–124. [CrossRef]

71. Woolard, F.X.; Moore, R.E.; Roller, P.P. Halogenated acetic and acrylic acids from the red alga Asparagopsis taxiformis. Phytochemistry 1977, 18, 617–620. [CrossRef]

72. Marshall, R.A.; Hamilton, J.T.G.; Dring, M.J.; Harper, D.B. Do vesicle cells of the red alga Asparagopsis (Falkenbergia stage) play a role in bromocarbon production? Chemosphere 2003, 52, 471–475. [CrossRef]

73. McConnell, O.; Fenical, W. Halogen chemistry of the red alga Asparagopsis. Phytochemistry 1977, 16, 367–374. [CrossRef]

74. Woolard, F.X.; Moore, R.E.; Roller, P.P. Halogenated acetic and acrylic acids from the red alga Asparagopsis taxiformis. Phytochemistry 1977, 18, 617–620. [CrossRef]

75. Kolsi, R.B.A.; Salah, H.B.; Hamza, A.; El Feki, A.; Allouche, N.; El Feki, L.; Belghith, K. Characterization and evaluating of antioxidant and antihypertensive properties of green alga (Codium fragile) from the coast of Sfax. J. Pharmacogn. Phytochem. 2017, 6, 186–191.

76. Ortiz, J.; Uquiche, E.; Robert, P.; Romero, N.; Quitral, V.; Llantén, C. Functional and nutritional value of the Chilean seaweeds Codium fragile, Gracilaria chilensis and Macrocystis pyriforma. Eur. J. Lipid Sci. Technol. 2009, 320–327. [CrossRef]

77. Santos, S.A.O.; Vilela, C.; Freire, C.S.R.; Abreu, M.H.; Rocha, S.M.; Silvestre, A.J.D. Chlorophyta and Rhodophyta macroalgae: A source of health promoting phytochemicals. Food Chem. 2015, 183, 122–128. [CrossRef] [PubMed]

78. Casas, M.P.; Rodríguez-Hermida, V.; Páez-Larrán, P.; Conde, E.; Liveri, M.T.; Ribeiro, D.; Fernandes, E.; Domínguez, H. In vitro bioactive properties of phlorotannins recovered from hydrothermal treatment of Sargassum muticum. Sep. Purif. Technol. 2016, 167, 117–126. [CrossRef]

79. Kendel, M.; Barnathan, G.; Fleurence, J.; Rabesoastra, V.; Wielgosz-Collin, G. Non-methylene interrupted and hydroxy fatty acids in polar lipids of the alga Grateloupia turuturu over the four seasons. Lipids 2013, 48, 535–545. [CrossRef]
80. Kendel, M.; Couzinot-Massion, A.; Viau, M.; Fleurence, J.; Barnathan, G.; Wielgosz-Collin, G. Seasonal composition of lipids, fatty acids, and sterols in the edible red alga Grateloupi turuturu. J. Appl. Phycol. 2013, 25, 425–432. [CrossRef]

81. Lee, J.B.; Ohta, Y.; Hayashi, K.; Hayashi, T. Immunostimulating effects of a sulfated galactan from Codium fragile. Carbohydr. Res. 2010, 345, 1452–1454. [CrossRef] [PubMed]

82. Shi, Q.; Wang, A.; Lu, Z.; Qin, C.; Hu, J.; Yin, J. Overview on the antiviral activities and mechanisms of marine polysaccharides from seaweeds. Carbohydr. Res. 2017, 453–454, 1–9. [CrossRef] [PubMed]

83. Fernández, P.V.; Arata, P.X.; Ciancia, M. Polysaccharides from Codium Species; Elsevier: Amsterdam, The Netherlands, 2014; Volume 71, ISBN 9780124080621.

84. Yang, Y.; Park, J.; You, S.G.; Hong, S. Immuno-stimulatory effects of sulfated polysaccharides isolated from Codium fragile in olive flounder, Paralichthys olivaceus. In Fish Shellfish Immunology; Elsevier Inc.: Alpharetta, GA, USA, 2019; Volume 87, pp. 609–614. [CrossRef]

85. Zhang, W.; Hwang, J.; Park, H.; Lim, S.; Go, S. Human Peripheral Blood Dendritic Cell and T Cell Activation by Codium fragile Polysaccharide. Mar. Drugs 2020, 18, 535. [CrossRef] [PubMed]

86. Sánchez-Camargo, P.; Montero, L.; Stiger-pouvreau, V.; Tanniou, A.; Cifuentes, A.; Herrero, M.; Ibáñez, E. Considerations on the use of enzyme-assisted extraction with pressurized liquids to recover bioactive compounds from algae. Food Chem. 2016, 192, 67–74. [CrossRef] [PubMed]

87. Flores-Fernández, N.; Domínguez, H.; Torres, M.D. A green approach for alginate extraction from Sargassum muticum brown seaweed using ultrasound-assisted technique. Int. J. Biol. Macromol. 2019, 124, 451–459. [CrossRef]

88. Martínez-Lüscher, J.; Holmer, M. Potential effects of the invasive species Gracilaria vermiculophylla on Zostera marina metabolism and survival. Mar. Environ. Res. 2010, 69, 345–349. [CrossRef]

89. Pereira, L. Edible Seaweeds of the World; CRC Press: Boca Raton, FL, USA, 2016.

90. Cardoso, I.; Cotas, J.; Rodrigues, A.; Ferreira, D.; Osório, N.; Pereira, L. Extraction and analysis of compounds with antibacterial potential from the red alga Grateloupi turuturu. J. Mar. Sci. Eng. 2019, 7, 220. [CrossRef]

91. Sheu, J.; Huang, S.; Duh, C. Cytotoxic Oxygenated Desmosterols of the Red Alga Galaxaura marginata. J. Nat. Prod. 1996, 59, 23–26. [CrossRef] [PubMed]

92. Pinteus, S.; Lemos, M.F.L.; Alves, C.; Silva, J.; Pedrosa, R. The marine invasive seaweeds Asparagopsis armata and Sargassum muticum as targets for greener antifouling solutions. Sci. Total Environ. 2021, 750, 141372. [CrossRef] [PubMed]

93. Pinteus, S.; Lemos, M.F.L.; Simões, M.; Alves, C.; Silva, J.; Gaspar, H.; Martins, A.; Rodrigues, A.; Pedrosa, R. Marine invasive species for high-value products’ exploration—Unveiling the antimicrobial potential of Asparagopsis armata against human pathogens. Algal Res. 2020, 52, 102091. [CrossRef] [PubMed]

94. Lee, C.; Park, G.H.; Ahn, E.M.; Kim, B.A.; Park, C.I.; Jang, J.H. Protective effect of Codium fragile against UVB-induced pro-inflammatory and oxidative damages in HaCaT cells and BALB/c mice. Fitoterapia 2013, 86, 54–63. [CrossRef]

95. Kim, A.D.; Lee, Y.; Kang, S.H.; Kim, G.Y.; Kim, H.S.; Hyun, C.-G. Jeju seaweeds suppress lipopolysaccharide-induction of pro-inflammatory and oxidative damages in HaCaT cells and BALB/c mice. Food Chem. Toxicol. 2016, 93, 69–77. [CrossRef] [PubMed]

96. Ganesan, P.; Matsubara, K.; Ohkubo, T.; Tanaka, Y.; Noda, K.; Sugawara, T.; Hirata, T. Anti-angiogenic effect of siphonaxanthin from Sargassum muticum brown seaweed against human umbilical vein endothelial cells. Molecules 2020, 25, 86. [CrossRef] [PubMed]

97. Silva, J.; Martins, A.; Alves, C.; Pinteus, S.; Gaspar, H.; Alfonso, A.; Pedrosa, R. Natural Approaches for Neurological Disorders-The Neuroprotective Potential of Mycosporine-Like Amino Acids from Gracilaria vermiculophylla (Rhodophyta) Cultured Through One Year in an Integrated Multi-trophic Aquaculture (IMTA) System. Mar. Biotechnol 2017, 19, 246–254. [CrossRef] [PubMed]

98. Le Guillard, C.; Dumay, J.; Donnay-Moreno, C.; Brzac, S.; Ragon, J.Y.; Fleurence, J.; Bergé, J.P. Ultrasound-assisted extraction of R-phycoerythrin from Grateloupi turuturu with and without enzyme addition. Algal Res. 2015, 12, 522–528. [CrossRef]

99. Sábeena Farvin, K.H.; Jacobsen, C. Phenolic compounds and antioxidant activities of selected species of seaweeds from Danish coast. Food Chem. 2013, 138, 1670–1681. [CrossRef] [PubMed]
106. Zubia, M.; Fabre, M.; Deslandes, E.; Shannon, C. Antioxidant and cytotoxic activities of some red algae (Rhodophyta) from Brittany coasts (France). *Botonica Mar.* 2009, 52, 268–277. [CrossRef]

107. Klejduš, B.; Plaza, M.; Snobllová, M.; Lojková, L. Development of new efficient method for isolation of phenolics from sea algae prior to their rapid resolution liquid chromatographic—tandem mass spectrometric determination. *J. Pharm. Biomed. Anal.* 2017, 135, 87–96. [CrossRef] [PubMed]

108. Balboa, E.M.; Luisa, M.; Nogueira, D.R.; González-lópez, N.; Conde, E.; Moure, A.; Pilar, M. Potential of antioxidant extracts produced by aequous processing of renewable resources for the formulation of cosmetics. *Ind. Crop. Prod.* 2014, 58, 104–110. [CrossRef]

109. Agregán, R.; Munekata, P.E.S.; Franco, D.; Dominguez, R.; Carballo, J.; Lorenzo, J.M. Phenolic compounds from three brown seaweed species using LC-DAD—ESI-MS/MS. *Food Res. Int.* 2017, 99, 979–985. [CrossRef] [PubMed]

110. Casas, M.P.; Conde, E.; Dominguez, R.; Moure, A. Ecofriendly extraction of bioactive fractions from *Sargassum muticum*. *Process Biochem.* 2019, 79, 166–173. [CrossRef]

111. Pérez-Larrán, P.; Torres, M.D.; Flórez-Fernández, N.; Balboa, E.M.; Moure, A.; Dominguez, H. Green technologies for cascade extraction of *Sargassum muticum* bioactives. *J. Appl. Physiol.* 2019, 31, 2481–2495. [CrossRef]

112. Mata, L.; Silva, J.; Schuenhoff, A.; Santos, R. The effects of light and temperature on the photosynthesis of the *Asparagopsis armata* tetrasporophyte (Falkenbergia rufolanosa), cultivated in tanks. *Aquaculture* 2006, 252, 12–19. [CrossRef]

113. Jacinto, M.S.C.; Monteiro, H.R.; Lemos, M.F.L. Impact of the invasive macroalga *Asparagopsis armata* on coastal environments: An ecotoxicological assessment. *Curr. Opin. Biotechnol.* 2013, 24S, S75. [CrossRef]

114. De Nys, R.; Steinberg, P.D.; Willemsen, P.; Dworjanyn, S.A.; Gabelish, C.L.; King, R.J. Broad spectrum effects of secondary metabolites from the red alga *delisea pulchra* in antifouling assays. *Biofuelling* 1995, 8, 259–271. [CrossRef]

115. Schuenhoff, A.; Mata, L.; Santos, R. The tetrasporophyte of *Asparagopsis armata* as a novel seaweed biofilter. *Aquaculture* 2006, 252, 3–11. [CrossRef]

116. Paul, N.; Nys, R. De Chemical defence against bacteria in the red alga *Asparagopsis armata*: Linking structure with function. *Mar. Ecol. Prog. Ser.* 2006, 306, 87–101. [CrossRef]

117. Choi, J.H.; Sapkota, K.; Park, S.E.; Kim, S.; Kim, S.J. Thrombolytic, anticoagulant and antiplatelet activities of codiase, a bi-functional fibrinolytic enzyme from *Codium fragile*. *Biochimica* 2013, 95, 1266–1277. [CrossRef]

118. Allhazzaa, R.; Nichols, P.D.; Carter, C.G. Sustainable alternatives to dietary fish oil in tropical fish aquaculture. *Rev. Aquac.* 2019, 11, 1195–1218. [CrossRef]

119. Umut, V.; Sivagnanam, S.P.; Rajauria, G.; O’Donnell, C.; Tiwari, B.K. Advances in pre-treatment techniques and green extraction technologies for bioactives from seaweeds. *Trends Food Sci. Technol.* 2021, 110, 90–106. [CrossRef]

120. Picot-Allain, C.; Mahomoodally, M.F.; Ak, G.; Zengin, G. Conventional versus green extraction techniques—A comparative perspective. *Curr. Opin. Food Sci.* 2021. [CrossRef]

121. Mendes, M.; Pereira, R.; Sousa Pinto, I.; Carvalho, A.P.; Gomes, A.M. Antimicrobial activity and lipid profile of seaweed extracts from the North Portuguese Coast. *Int. Food Res. J.* 2013, 20, 3337–3345.

122. Kamarudin, A.A.; Mohd, E.N.; Saad, N.; Sayuti, N.H.; Nor, N.A. Heat assisted extraction of phenolic compounds from *Eleutherine bulbosa* (Mill.) bulb and its bioactive profiles using response surface methodology. *Ind. Crops Prod.* 2020, 144, 112064. [CrossRef]

123. Genovese, G.; Gedone, L.; Hamann, M.T.; Morabito, M. The Mediterranean Red Alga *Asparagopsis*: A Source of Compounds against Leishmania. *Mar. Drugs* 2009, 7, 361–366. [CrossRef] [PubMed]

124. Custódio, L.; Silvestre, L.; Rocha, M.I.; Rodrigues, M.J.; Vizetto-duarte, C.; Pereira, H.; Barreira, L.; Varela, J.; Custódio, L.; Silvestre, L.; et al. Methanol extracts from *Cystoseira tamariscifolia* and *Cystoseira nodiculais* are able to inhibit cholinesterases and protect a human dopaminergic cell line from hydrogen peroxide- induced cytotoxicity from hydrogen peroxide-induced cytotoxicity. *Pharm. Biol.* 2016, 54, 1687–1696. [CrossRef]

125. Kang, C.-H.; Choi, Y.H.; Park, S.-Y.; Kim, G.-Y. Anti-Inflammatory Effects of Methanol Extract of *Codium fragile* in Lipopolysaccharide-Stimulated RAW 264.7 Cells. *J. Med. Food* 2011, 15, 44–50. [CrossRef]

126. Dilishara, M.G.; Jayasooriya, R.G.P.; Kang, C.H.; Choi, Y.H.; Kim, G.Y. Methanol extract of *Codium fragile* inhibits tumor necrosis factor-α-induced matrix metalloproteinase-9 and invasiveness of MDA-MB-231 cells by suppressing nuclear factor-κB activation. *Asian Pac. J. Trop. Med.* 2016, 9, 535–541. [CrossRef]

127. Lee, S.A.; Moon, S.M.; Choi, Y.H.; Han, S.H.; Park, B.R.; Choi, M.S.; Kim, J.S.; Kim, Y.H.; Kim, D.K.; Kim, C.S. Aqueous extract of *Codium fragile* suppressed inflammatory responses in lipopolysaccharide-stimulated RAW264.7 cells and carrageenan-induced rats. *Biomed. Pharmacother.* 2017, 93, 1055–1064. [CrossRef]

128. Yoon, H.-D.; Jeong, E.-J.; Choi, J.-W.; Lee, M.-S.; Park, M.-A.; Yoon, N.-Y.; Kim, Y.-K.; Cho, D.-M.; Kim, J.-I.; Kim, H.-R. Anti-inflammatory Effects of Ethanolic Extracts from *Codium fragile* on LPS-Stimulated RAW 264.7 Macrophages via Nuclear Factor kappaB Inactivation. *Fish. Aquat. Sci.* 2012, 14, 267–274. [CrossRef]

129. Moon, S.M.; Lee, S.A.; Han, S.H.; Park, B.R.; Choi, M.S.; Kim, J.S.; Kim, S.G.; Kim, H.J.; Chun, H.S.; Kim, D.K.; et al. Aqueous extract of *Codium fragile* alleviates osteoarthritis through the MAPK/NF-κB pathways in IL-1β-induced rat primary chondrocytes and a rat osteoarthritis model. *Biomed. Pharmacother.* 2018, 97, 264–270. [CrossRef]
153. Mulvaney, W.J.; Winberg, P.C.; Adams, L. Comparison of macroalgal (Ulva and Grateloupia spp.) and formulated terrestrial feed on the growth and condition of juvenile abalone. *J. Appl. Phycol.* 2013, 25, 815–824. [CrossRef]

154. García-Bueno, N.; Turpin, V.; Cogne, B.; Dumay, J.; Morançais, M.; Amat, M.; Pédron, J.-M.; Atucha, A.M.; Fleurence, J.; Decottignies, P. Can the European abalone Haliotis tuberculata survive on an invasive algae? A comparison of the nutritional value of the introduced Grateloupia turuturu and the native Palmaria palmata, for the commercial European abalone industry. *J. Appl. Phycol.* 2016, 28, 2427–2433. [CrossRef]