



# **Macroalgae Biorefinery for the Cosmetic Industry: Basic Concept, Green Technology, and Safety Guidelines**

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Abstract: With the growth in the number of people searching for ways to improve personal care, the consumer finds the solution in cosmetic products. However, this demand is currently made concomitantly with the demand for products of natural origin, including seaweed. Algae, in their composition, are full of bioactive compounds with several applications. Therefore, their insertion in cosmetics is evidenced in the high number of scientific studies, which makes this natural resource potentially useful for the cosmetic industry. From this, a review was conducted with the aim of highlighting some of these active compounds and the latent applicability and versatility of others. In addition, the best way to add to the production of these substances while staying in alignment with green consumption, the design of biorefineries, and the promising production of macroalgae on a large scale using green technologies was sought.

Keywords: algae; industry; cosmetics; green technologies; guidelines



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## 1. Introduction

In recent years, concerns about the environment and the wellness of society have been driving industry demands for natural products. This behavior has encouraged private and public investments into research on the extensive use of renewable resources to produce more sustainable ingredients. Along with this demand, policies such as those from the European Commission [1] and the Blue Bioeconomy Forum [2], as well as international guidelines such as ISO 16128-2:2017 [3], are contributing to industry and other stakeholders achieving the Sustainable Development Goals (SDGs) outlined by the United Nations [4].

Among the renewable resources that show potential in the manufacture of innovative green ingredients for different economic activities are those from aquatic or marine environments [2]. They are underexploited resources despite the fact they have diverse high-added-value compounds with potential applications in food and feed and the cosmetic and pharmaceutical industries. Within the group of marine organisms, there are macroalgae rich in bioactive compounds that can be explored as functional ingredients. This diversity of components is due to the survival power of these marine algae in a competitive environment, which has led to them developing defense strategies from different metabolic pathways that result in a significant level of chemical–structural diversity [5]. Compounds with antioxidant activities, growth factors, anti-inflammatory agents, and pigment whitening indicate some of the different functions algae can provide for the most diverse products (Table 1).

Cosmetics have been applied from ancient times in many civilizations for artistic, embellishment, protective, cleaning, and ceremonial purposes. The word cosmetic is derived from the Greek kosmetikos, which means having the power to skillfully organize decorations, as well as from kosmein, which means adorn, and kosmos, which means order and harmony; however, the true origin of cosmetics is probably even more grounded in antiquity because the first rock paintings of 30,000 years ago portray the use of bodily

adornments (rudimentary cosmetics) in the rituals of mating and hunting [6]. Alexander the Great (356–323 a. C.) reported the use of ointments, incense, and other cosmetics by the countries of the Indo-Sumerian civilization [7]; therefore, cosmetics have been a part of the cultures of different civilizations.

Over the years, the skin has received special care and attention from industry, becoming a market rated at EUR 80 billion in 2016 in terms of retail sales in the European market, followed closely by the American (EUR 64 billion) and Brazilian (EUR 24 billion) markets; according to trends, these values will only increase. This industry is always searching for new ingredients for two main reasons: the first being the obvious marketing advantage, and the second being a result of needing to replace raw materials that have either been banned or become less trusted by consumers throughout the decades [8], with macroalgae being the target of the moment when it comes to innovation in ingredients and efficiency in this area.

## 2. Overview of Marine Macroalgae Chemical Composition and Bioactivities

The phylum classification of marine macroalgae concerns the prevalence of their pigments, i.e., fucoxanthin for brown (Phaeophyceae), phycobiliproteins for red (Rhodophyta), and chlorophyll for green (Chlorophyta) algae. According to AlgaeBase [9], there are 168,376 species and intraspecific names of algae (macroalgae and microalgae). However, only a few species are raw materials for industry due to the lesser-known bioactivity of ingredients that can be extracted from macroalgae (Table 1).

Carbohydrates and lipids are structural molecules and part of the primary metabolism of macroalgae. Both molecule classes are commercially explored and receive great interest from the food, cosmetic, and pharmaceutical industries since they include polysaccharides (such as agar, carrageenan, fucoidan, and alginates) and long-chain polyunsaturated fatty acids (such as omega-3 docosahexaenoic acid and eicosapentaenoic acid). In recent years, because of the rising interest in non-animal protein, macroalgae have also been explored as a renewable source of protein and have a forecasted market value of USD 1.51 billion for 2030 [10].

Besides these molecules, much of the bioactivities of macroalgae extracts originate from secondary metabolism compounds that are often found at trace levels of detectability. Bioactivity can also be derived from synergies between compounds within an extract, and, in some cases, not being a derived property of any individual compound present in the extract can result in this effect being lost through compound separation and purification [11].

Putative Efficacies/Activities	Polysaccharides	PUFAs	Mycosporine-like Amino Acids	Phenolic Compounds	Pigments	Sterols
Anti-acne					[12]	
Anti-inflammatory	[13–16]	[15,17]	[15,17,18]	[15,17,19]	[17,18]	[20]
Anti-photoaging	[17–19,21]		[18]	[17]	[18,22]	[20]
Anti-skin aging	[16,23]			[23]		[24]
Anti-wrinkling	[16,23,25]			[26]		
Antiapoptotic	[21,27]			[28]		
Antioxidant	[19,25,27,29]		[18]	[17,19,23,29]	[17–19]	[17]
Antipollution				[28]		
Depigmenting,						
bleaching, and	[16,19,23,29]			[17,26,29]	[17]	
lightening						
Hair growth				[29]		
Hydration	[29]			[29]		
Photoprotection	[29]		[17,18]	[17,29]	[17,18]	
Skin barrier	[19]		- / -		[18]	
Wound healing	[30,31]					

Table 1. Putative efficacy of some chemical classes from macroalgae.

## 2.1. Polysaccharides

Polysaccharides are the most significant and beneficial compounds in macroalgae for industry and are present in many different types of macroalgae, such as agar, carrageenan, laminarin, alginates, and ulvan [32]. The main macroalgae polysaccharides are sulfated, though in addition to these the group also includes alginates (1), fucoidan (2), and laminarin (3) in brown macroalgae, agar (4) and carrageenan (5) in red macroalgae, and ulvan (6) in green macroalgae (Figure 1). Moreover, they have a wide variety of bioactivities that may have applications in the cosmetic industry due to anti-inflammatory, anti-photoaging, anti-skin aging, anti-wrinkling, antiapoptotic, antioxidant, depigmenting, bleaching, lightening, hydration, photoprotection, skin barrier, and wound healing properties (Table 1). One of the most important functional requirements of polysaccharides is that they must be stable during industrial processes when presented with the conventional method of alkaline extraction, where they are subjected to conditions such as high temperature and various Ph levels and ionic strengths [33].

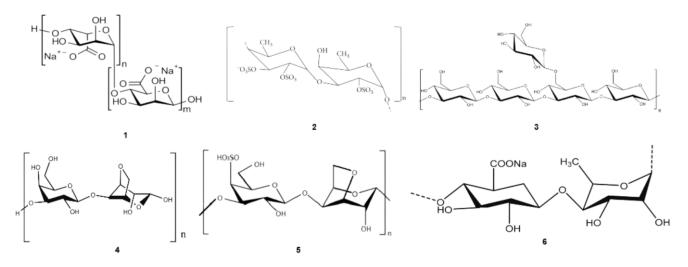


Figure 1. Polysaccharides from macroalgae.

#### 2.2. Polyunsaturated Fatty Acids (PUFAs)

The physical and biochemical characteristics of PUFAs play an essential role in the survival and growth of microorganisms and aquatic animals in some hostile environments. They are a primary source for the metabolism of these organisms, participating as a structural component of cell membranes. The concentrations of these PUFAs also vary according to temperature, environment, and season of the year, with lower temperatures favoring their production. Among these compounds (omega-3, omega-6, and omega-9), long-chain omega-3 fatty acids are of great interest to industry, including eicosapentaenoic acid (EPA) (7) and docosahexaenoic acid (DHA) (8) (Figure 2). PUFAs are essential for the human diet and are mainly used in the food and pharmaceutical industries. This is because an omega-6/omega-3 ratio of 3:4 is advised for health benefits related to their consumption [34]. Likewise, the World Health Organization recommends an omega-6/omega-3 ratio of up to 10:1 [35].

Otero et al. [36] evaluated several macroalgae from the northwest of Spain, including the brown *Fucus vesiculosus* and green *Ulva lactuta* algae, and subjected them to liquid extraction to obtain high-quality fatty acids, including omega-3 fatty acids. Besides application as a nutraceutical, the authors found relevant antioxidant and antimicrobial activities. The same study also found substances isolated from macroalgae with potent antimicrobial activity, including polysaccharides, fatty acids, phlorotannins, pigments, lectins, alkaloids, terpenoids, and halogenated compounds; therefore, several compounds are involved in this activity, including these fatty acids.

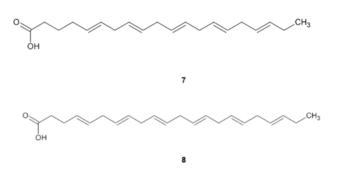


Figure 2. Polyunsaturated Fatty Acids from macroalgae.

Considering the search for new natural preservatives, these findings indicate potential applications in the cosmetic industry. However, there are only a few studies on PUFAs and skincare cosmetics (Table 2).

Table 2. Examples of macroalgae extracts used as ingredients by the cosmetic industry.

International Nomenclature of Cosmetic Ingredients (INCI) Name	Type (Color)	Ingredient Name	INCI Functions
Hypnea musciformis Extract	Rhodophyta	Algae hypnea contains alginic acid, mannitol, carrageenan, galactosides, amino acids, mineral salts, oligoelements, vitamins, and pigments	skin protection
Gelidiella acerosa Extract	Rhodophyta	<i>Hypnea Musciformis</i> Extract (and) <i>Gelidiella Acerosa</i> Extract (and) <i>Sargassum Filipendula</i> Extract (and) Sorbitol	skin protection
Sargassum filipendula Extract	Phaeophyceae	<i>Hypnea Musciformis</i> Extract (and) <i>Gelidiella Acerosa</i> Extract (and) <i>Sargassum Filipendula</i> Extract (and) Cellulose	skin protection
Gymnogongrus durvillei (formerly Ahnfeltiopsis concinna) Extract	Rhodophyta	Ahnfeltia Concinna Extract	viscosity control
Botryocladia occidentalis Extract	Rhodophyta	Water (and) Botryocladia Occidentalis Extract (and) Hypnea Musciformis Extract (and) Sargassum Vulgare Extract	skin conditioning
Chondrus crispus Extract	Rhodophyta	Chondrus Crispus Extract	film-forming, skin-smoothing, and moisturizing properties, viscosity control
Ascophyllum nodosum Extract	Phaeophyceae	Ascophyllum nodosum Extract	skin conditioning, may help protect against UVB ray
Laminaria ochroleuca Extract	Phaeophyceae	Caprylic/Capric Triglyceride (and) <i>Laminaria ochroleuca</i> Extract	skin conditioning
<i>Kappaphycus alvarezii</i> Extract (Telosomyl)	Rhodophyta	Water (and) <i>Kappaphycus alvarezii</i> Extract (and) <i>Laminaria saccharina</i> Extract (and) Hydrolyzed Rice Protein	skin conditioning
<i>Laminaria digitata</i> Extract (Horsetail Kelp Extract)	Phaeophyceae	Aqua (and) Propylene Glycol (and) <i>Laminaria digitata</i> Extract	skin protection

International Nomenclature of Cosmetic Ingredients (INCI) Name	Type (Color)	Ingredient Name	INCI Functions
Neopyropia yezoensis (formerly Porphyra yezoensis) Extract	Rhodophyta	Water (and) Butylene Glycol (and) Porphyra yezoensis Extract	skin conditioning
<i>Eisenia bicyclis</i> Extract	Phaeophyceae	Aqua, Aloe Barbadensis, Cocos Nucifera Milk, Melaleuca Oil, Cucumis Sativus, Anthemis Nobilis, Hyaluronic Acid, Camellia Sinensis, Xanthan Gum, <i>Arame algae</i> Extract, Vitis Vinifera, Matricaria Chamomilla, C, Betaine, Lavender Extract, Citrus Sinensis, Camellia Sinensis, Mangifera Indica, Leuconostoc Radish Root Ferment Filtrate, Tetrasodium Glutamate Diacetate	skin conditioning, skin protection, anti-inflammatory effects, soothing effect
Ecklonia cava Extract	Phaeophyceae	Ecklonia cava Extract	skin conditioning agent
Eisenia arborea Extract	Phaeophyceae	Water, Butylene Glycol, Eisenia arborea Extract	skin conditioning agent
Gracilariopsis longissimaf (ormerly Gracilaria verrucosa) Extract	Rhodophyta	Gracilaria verrucosa Extract	humectant, skin protection, production of agar, potential antiseptic function for human skin
Porphyra umbilicalis Extract	Rhodophyta	Aqua (and) Lecithin (and) Alcohol (and) Sodium Lactate (and) <i>Porphyra umbilicalis</i> Extract (and) Phenoxyethanol	skin conditioning agent
Codium tomentosum Extract	Chlorophyta	Propylene Glycol (and) Aqua (and) Codium tomentosum Extract	skin protection
Fucus vesiculosus Extract (Bladderwrack)	Phaeophyceae	Fucus vesiculosus Extract	emollient, skin conditioning, smoothing, soothing
Pelvetia canaliculata Extract	Phaeophyceae	Aqua (and) <i>Pelvetia</i> <i>canaliculata</i> Extract	skin protection
Caulerpa racemosa Extract	Chlorophyta	Caulerpa racemosa Extract	skin conditioning
<i>Furcellaria lumbricalis</i> Extract	Rhodophyta	<i>Furcellaria lumbricalis</i> Extract and <i>Perna canaliculus</i> Extract	skin conditioning
Ulva lactuca Extract	Chlorophyta	Glycerin (and) Aqua (and) Hydrolyzed <i>Ulva lactuca</i> Extract	skin conditioning, skin protection
Saccharina japonica Extract	Phaeophyceae	Saccharina japonica Extract	skin conditioning
Cladosiphon okamuranus Extract	Phaeophyceae	Cladosiphon okamuranus Extract	skin conditioning
Sargassum vulgare Extract	Phaeophyceae	Water (and) Botryocladia occidentalis Extract (and) Hypnea musciformis Extract (and) Sargassum vulgare Extract	skin conditioning

Table 2. Cont.

Phaeophyceae (brown algae), Chlorophyta (green algae), Rhodophyta (red alga).

## 2.3. Mycosporine-like Amino Acids (MAAs)

When exposed to UV radiation, macroalgae synthesize different defense mechanisms to deal with the radiation. One of these mechanisms is the release of mycosporine-like amino acids (MAAs), which consist of a cyclohexenimine ring conjugated with two amino

acids, amino alcohol, or amino group substituents [37]. These compounds can dissipate absorbed radiation as harmless heat without producing reactive oxygen species (ROS). This characteristic makes them suitable as an option for sunscreens and they also provide additional protection in the form of antioxidants [38]. Furthermore, the antioxidant activity of seaweed-derived MAAs such as porphyra-334 (9), shinorine (10), asterina-330 (11), palythine (12), and mycosporine-glycine (Myc-Gly) (13) (Figure 3) has been tested in various assays [18]. These photoprotective compounds have been isolated from various macroalgal species, mainly in Rhodophyta [39], and exhibit maximum UV absorption between 310 and 362 nm [40]. Notably, these MAAs are considered the greatest absorbers of UVA in nature, and some of them can even act as antioxidants [41]

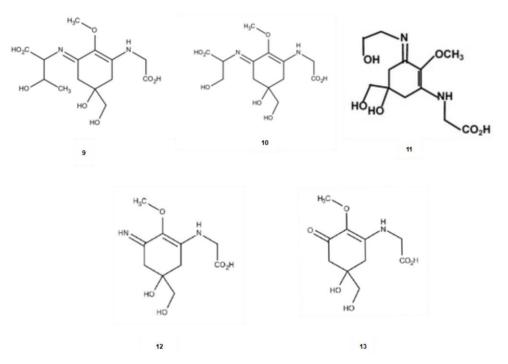


Figure 3. Mycosporine-like Amino Acids from macroalgae.

#### 2.4. Phenolic Compounds

These macroalgae are rich in various phenolic compounds, such as catechins (14), flavonols (15), flavonolglycosides (16), phloroglucinol (17), gallic acid (18), epicatechin (19), pyrocatechol (20), gallate (21), flavonoids (22), anthocyanins (23), stilbenes (24), lignans (25), and phenolic polymers (26) [16] (Figure 4). Phenols and flavanols have already been described as having antioxidant activity through tests including the ABTS radical scavenging assay and the DPPH radical scavenging assay. Considering that, from a chemical point of view, phenolic compounds are formed by a structural nucleus based on a hydroxyl group linked directly to phenol, and that this configuration gives them the ability to capture free radicals, reactive oxygen species, and chelated metal ions [42], it is to be expected that their action as an antioxidant, anti-inflammatory agent, and immune system modulators is obtained and maintained through extraction and isolation from macroalgae. This formation of chelates is an antioxidant mechanism of flavonoids, where flavonoids containing a carbonyl group in position four and a hydroxyl group in position three or five, such as quercetin, rutin, kaempferol, myricetin, or morphine, form chelates with metal ions. This ability to sequester metal ions may contribute to their antiperoxidative properties by preventing the formation of free radicals (Cook and Samman, 1996). Beyond that, some substances are derived from these phenolic compounds. This includes tannins, a phenolic acid, and within this group, phlorotannins (27). Phlorotannins are a type of tannins found in brown algae such as kelps, rockweeds, or Sargassaceae species, and they are also found

in a lower amount in some red algae. These substances play a role as inducible screens that protect against harmful UV radiation and also exhibit antioxidant activity [43].

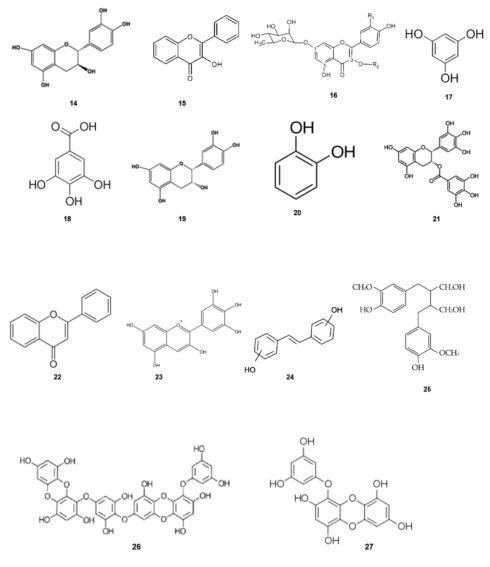


Figure 4. Phenolics from macroalgae.

Phenolics also have a photoprotective function, as shown in macroalgae that improve the production of UV-absorbing (phenolic) compounds through exposure to UV, thus mitigating and even preventing damage. This only supports the results obtained by Polo and Chow [44] on the *Sargassum felipendula* (Phaeophyceae) extract, which, when subjected to radiation, tends to have high antioxidant potential. This is because the alga is expected to develop a very effective antioxidant defense system for their survival due to the strong UV incidence. It is not by chance that this extract and this genus are used as a skin protection agent (Table 2).

According to Tsao [45], flavonoids are the largest and most diverse group of bioactive natural products categorized under the family of polyphenols, and green algae represent the most primitive type of plant species that contain them. As they are present in this family of polyphenols, they are listed as UV-protecting antioxidants and anti-predatory toxicants; however, when dealing specifically with flavonoids in algal species, their bioactive properties remain underexplored [21].

However, plant species and their flavonoid-rich extracts have been studied in dermatology and cosmetic preparations due to their strong antioxidant, anti-inflammatory, antimicrobial, and affinity/inhibition effects concerning specific enzymes that promote inflammation [46]; thus, flavonoids from algae also have this action potential.

A study by Castejon et al. [47] screened the potential cosmetic applications of aqueous extracts of three Icelandic algae, including *Ulva lactuca*, and evaluated the content of polyphenols, flavonoids, and carbohydrates. With the results, they were able to observe high levels of these bioactive compounds in correlation with flavonoid activity, despite evidence being scarce in the literature. They saw that their use in skin whitening and antiaging products is positive, since they suggest that tyrosinase inhibitory activity is positively correlated with flavonoid and phenolic content. It is noteworthy that tyrosinase plays an important role in the biosynthesis of the pigment melanin in the skin [48]. This melanin protects from harmful ultraviolet radiation, which can create aesthetic problems when accumulated, such as the famous hyperpigmented spots [49]. Consequently, the attachment of tyrosinase inhibitors in cosmetics can be attractive due to the lightening effects.

#### 2.5. Pigments

In addition to the compounds mentioned previously, macroalgae contain a broad range of photosynthetic pigments, chlorophylls (28), carotenoids (29) (carotenes, xanthophylls, fucoxanthin, and peridinin), and phycobiliproteins (30) (phycocyanin and phycoerythrin) (Figure 5) [50]. For example, carotenoids are photoreceptors in algae that absorb light energy and transport it to the electron transport chain. In addition to this function, they protect chloroplasts from excess light radiation and reactive species generated during oxygen-evolving photosynthesis [51]; therefore, with an attributed antioxidant function of interest to cosmetics, they have also been used as stabilizers and as preservatives in creams and lotions for solar protection [52]. These pigments are algae-derived metabolites and they have a diversified profile that can be applied in various applications, such as in anti-acne, anti-inflammatory, anti-photoaging, antioxidant, depigmenting, bleaching, lightening, photoprotection, and skin barrier products that protect against excess solar radiation (Table 1).

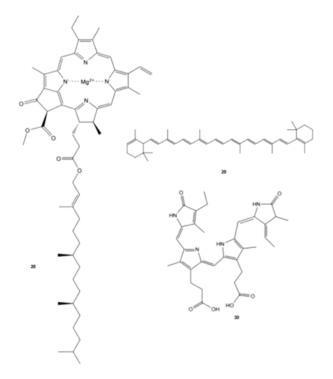


Figure 5. Pigments from macroalgae.

#### 2.6. Sterols

Another group of important bioactive substances obtained from algal sources is sterols, which are present in the cell membrane and influence cell functions. They are found in many forms, including as free sterols (31), sterol esters (32), alkyl sterol ethers (33), sterol sulfates (34), or linked to a glycosidic moiety (35) (Figure 6) [53]. However, despite their consistent presence, sterols are found in distinctly different compositions across kingdoms and among algae.

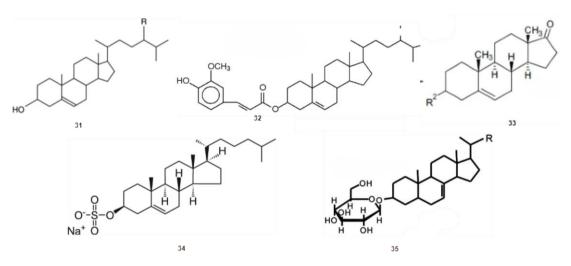


Figure 6. Sterols from macroalgae.

Regarding functionality, most studies report that foods containing these sterols can lead to decreased absorption of cholesterol and reduced serum levels of low-density lipoprotein cholesterol [54], which is beneficial for human health. In the case of cosmetics, sterols are used as hydrating agents that limit water loss through different mechanisms and are also used in conjunction with humectant substances on the skin's surface to attract water, which is a form of hydration. It has also been shown that macroalgae sterols have antiinflammatory, anti-photoaging, anti-skin aging, and antioxidant actions that the cosmetic industry may explore (Table 1).

## 3. The Application of Algae Extracts in Cosmetics

For the Food and Drug Administration (FDA) in the United States of America (USA), cosmetics are products that, when applied to the human body, cleanse, beautify, promote attractiveness, or modify the appearance of the skin, hair, or body without affecting its structure or function [55].

During the last decades, the toxicological safety of cosmetics and their ingredients has attracted increasing attention [56]. This is revealed when analyzing the growing amount of interest in products marketed under the label of "natural", and in the case of biodiversity, it gains strategic value over possible industrial and economic uses in different segments. Through this growing trend across the world, especially in European countries, the consumer market is increasingly engaging in campaigns of so-called "green consumption", that is, of products made based on natural activities, as in the case of those developed by the cosmetics industry [57].

Nowadays, in the cosmetic field, there are more concepts in this area, such as clean beauty that, in a nutshell, refers to skincare products that are clean of harmful ingredients. This sometimes indicates that clean beauty brands use natural ingredients while also still using synthetic ingredients deemed safe for consumers' health and the environment [58]. As the market moves towards minimalist beauty, today's consumer even demands that brands clean their products of potentially harmful substances to the environment in order to meet their expectations. From that idea arises the minimal formula, where skincare brands formulate products with fewer chemical ingredients, simple packaging, and intelligence, which is

the presence of technologies capable of communicating the real conditions of a product or the environment in which it is found. This makes them eco-friendly and sustainably provides comfort and transparency for consumers concerned about their environmental impact.

As aforementioned, macroalgae produce a wide variety of chemically active primary and secondary metabolites, with secondary metabolites being known for their main purpose of protection against abiotic and biotic stresses. These active metabolites, such as halogenated compounds, alcohols, aldehydes, and terpenoids, are produced by several species of marine macroalgae and have antibacterial and antifungal properties, making them suitable for use in therapeutics [59]. Furthermore, these metabolites allow these molecules to be explored and novel and natural bioactive compounds to be found.

Based on a search of industrial and commercial studies, it was observed that the main application of seaweed extracts in cosmetics is skincare (Table 2). They are established in the market for products for the face and skin, such as anti-aging and regenerating creams, refreshing products, emollients, anti-irritants, sun protection, and hair care products.

When looking for products that contain macroalgae extracts in their composition through the International Nomenclature of Cosmetic Ingredients (INCI), these extracts were identified in products of the following skincare categories: skin smoothing, viscosity control, skin conditioning, and skin protection. However, algae are useful in more than just skin products, with algae extracts also present in hair care and self-care products.

It is known that macroalgae have been used since the 19th century by Asian women in thalassotherapy. This important economic activity uses seawater and its products, including algae, as a form of therapy [60]. Therefore, the presence of algae in beauty rituals is nothing new, with algae boiled, ground, and applied to the skin and hair to restore the skin's plumpness and the natural shine of the hair. Initially, the products with algae incorporated into them were essentially soaps, shaving creams, shampoos, colorings, tonics, makeup items, foams, and other bath products. Over the years and with advances in research, their content in trace elements began to be considered and implemented.

Trace elements also include mineral salts, vitamins, and amino acids. All of them are useful for skincare and skin health as they are assimilated by skin cells. Because of this, the sea, especially seaweeds, has become a great source of new materials for incorporation into cosmetic formulations with the widest possible purposes, with potential applications in toning treatments, moisturizing treatments, and rejuvenating treatments.

To understand the important role of algae in cosmetics, it is necessary to understand what is meant by skin protection, viscosity control, skin conditioning, and skin smoothing. When it comes to skin smoothing, some ingredients are believed to be humectants that work by pulling water into the skin and retaining it, which are characteristics of ingredients based on hydrophilic substances. Hydrophilic carbohydrates are seaweed's main and abundant constituent and have been used in cosmetic formulations such as moisturizing and thickening agents (Kim et al. 2018). Polysaccharides, large and sometimes branched carbohydrates, can absorb water in the skin; therefore, they are used as moisturizing agents in cosmetology [61].

An emollient soothes the skin, filling in cracks. Therefore, emollients are mostly used for irritated, inflamed skin. Among substances with this characteristic, lipids and fatty acids are emollients. In addition, fatty acids can indirectly affect the stimulation of skin hydration and elasticity [62]. Given this, an ideal emollient should contain a combination of occlusive agents to delay water loss, humectants to increase moisture-holding capacity, and lubricants to reduce friction against the skin [63], which is found in seaweed extracts such as *Botryocladia occidentalis* (Rhodophyta) extract.

Viscosity is a rheological parameter that describes the propensity of a liquid to slide or flow on a surface; therefore, it represents the resistance to deformation caused by any tension, such as that caused by the application of a cream [64]. According to the INCI, viscosity control is the official function name for thickeners whose ingredients help thicken products, thus forming a pleasant gel, serum, or moisturizer texture. Macroalgae extracts such as *Gymnogongrus durvillei* (formerly *Ahnfeltiopsis concinna*) extract and *Chondrus crispus* (Rhodophyta) extract are natural thickeners that stabilize emulsions and even help with the effects of their bioactive properties. Regarding the skin, with the advancement of aging, a cycle of elasticity loss and increased viscosity begins. Therefore, skin hydration through the use of cosmetic and dermatological products can reduce the appearance of aging effects and momentarily improve skin elasticity.

Skin conditioning products are designed to reduce fine lines, hyperpigmentation, age spots, and skin laxity, all of which help improve skin. Different types of products include cleansers, topical vitamins, antioxidant products, and retinol products. This class of products can be seen in moisturizers, exfoliants, and different emulsions [65]. This includes the antioxidants present in the different macroalgae extracts used and the other trace elements they contain.

Regarding skin protectors, algae are a deposit of photoprotective substances, something that can be noticed in the database developed by Gröniger et al. [66]. Substances such as mycosporin-like amino acids (MAAs), sulfated polysaccharides, carotenoids, and polyphenols can be used for photoprotection and provide the skin with adequate protection against ultraviolet B (UVB)- and ultraviolet A (UVA)-induced photodamage [67].

It is interesting to note that in addition to these macroalgae substances already established in studies to have activities of interest for cosmetological application, there are further substances of industrial interest in macroalgae extracts. These same extracts can exhibit more activity due to possessing antibacterial peptides [68], as well as antifungal [69] and even antiviral [44] properties that can be used in skincare products to function as preservatives and bioactive compounds. Their use can also replace or even eliminate the need for synthetic products.

Nevertheless, the extraction process must be selected so that these compounds are not wasted in the process of obtaining them. Here, a combination of different green processing technologies emerges, which are the ideal choice for obtaining improvements in the algae extraction process, as well as in aspects related to the economy in various directions of production, including reductions in energy consumption and the transformation of waste into by-products. These green strategies therefore make the process an eco-friendly alternative that is already highly sought after.

#### 4. Production of Macroalgae Ingredients with Green Technology

Choosing which extraction method will be used for marine natural products is the first step and is also one of the most important in obtaining the compounds of interest. It is known that the most traditional products obtained by macroalgae are polysaccharides, often through high-temperature and alkaline extraction methods that need aggressive chemical reagents, high energy, and expensive time consumption. Despite recent technological advances (new techniques and protocols) that enable greener and more efficient extractions, there are still investments being made to improve traditional methods (Table 3).

These greener technologies improve yields, minimize solvent waste, save time and energy, and facilitate automation. Some examples include supercritical  $CO_2$  extraction, pressurized liquid extraction, subcritical water extraction, and microwave-assisted extraction [70]. These green technologies demand the use of renewable vegetable sources such as macroalgae in the development of processes that use less petroleum-based solvents or even replace them. Finally, these technologies also reduce costs by reducing the time required and the complexity of steps involved while optimizing operations and transforming waste into co-products or by-products [71].

**Table 3.** Representative International Patent Applications regarding the preparation of polysaccharides (International Patent Classification [IPC] main group: C08B 037/00) from seaweeds (2002 to 2022).

Polysaccharide (Phycocolloid)	Patent Number	Priority Date	Brief Description of Polysaccharide Preparation Methods
Non-specific	WO2021133148	27 December 2019	The present invention provides a method for separating polysaccharides from seaweed. The method for obtaining polysaccharides comprises a pre-treatment step that ages seaweed at 20–50 °C before extraction with a solvent to remove salts and color materials; an extraction step with hot water that removes the seaweed from which salts and color materials have been removed; a separation step where seaweed is categorized according to size; and a purification step at 40–60 °C.
Agar and Agarose	WO2010109289	24 March 2009	The present invention relates to a more convenient and energy-efficient process for the preparation of agarose from <i>Gracilaria</i> and <i>Gelidiella</i> spp. (Rhodophyta), more particularly <i>Gracilaria dura</i> and <i>Gelidiella acerosa</i> (Rhodophyta) from Indian waters. Said process comprises steps where the dry seaweed is pre-treated with alkali and then rinsed until a pH ranging between 7 and 9 is shown, with water then added before subsequent autoclaving to obtain the extract, which is then centrifuged before being treated with surface-active chemicals to induce the precipitation of agarose. This is followed by centrifugation of the mass to remove the adhering liquid, which is then rinsed with water to remove the surface-active chemical. A hot sol of the agarose is then prepared in a minimum quantity of water before the agarose is then re-precipitated with iso-propanol to achieve a gel product with dispersibility. The described gel showed performance equal to that of gel obtained through a more conventional process of agarose preparation in DNA gel electrophoresis studies involving the same seaweed extractives, as well as performance akin to that of gel prepared from a commercial benchmark.
Agar and Carrageenan	WO2015102021	30 December 2013	The present invention provides an integrated process for the recovery of a spectrum of commercially valuable products (including agar, cellulose, lipids, pigments, and liquid rich in minerals of agricultural importance) directly from fresh seaweed without employing any catalyst-driven in situ chemical conversions. Additionally, the solvents used during lipid extraction were capable of being used for three cycles without the yield and quality of successive products being affected. Furthermore, this new process is highly efficient and utilizes the total amount of raw seaweed material without any biomass leftover as solid waste.
Carragenan	WO2012123422	11 March 2011	The present invention relates to a method for processing fresh seaweed. This method relates to the use of the processed seaweed components in the food sector, in the pharmaceutical sector, as food supplements, in cosmetics, and also in animal husbandry as feedstuff, as well as to the products made using such a method.
Alginates	WO2022139115	22 December 2020	The present invention is designed to increase production efficiency and decrease the production costs of alginic acid and fucoidan. The method comprises the following steps: separating a mixture including ground sea algae, water, and an organic acid into a primary solid and liquid extraction; adding calcium chloride to the separate liquid to aggregate a secondary solid; separating the liquid containing the secondary solid aggregated therein into a secondary solid and residual liquid; extracting fucoidan from the residual liquid; and extracting alginic acid from the primary and secondary solid.
	WO2021090023	7 November 2019	The present invention relates to a method of processing macroalgae in which superheated solvent (water or alcohol [methanol, ethanol, or propanol] or water/alcohol mixtures) is used in an initial pre-treatment step (temperature range: 101 °C to 150 °C; pressure range: 105 kPa to 500 kPa). Polysaccharide extraction is carried out for up to 24 h in an alkali solution (sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, or sodium carbonate). To precipitate alginate from the previous solution, the alginate composition can be contacted with acid, calcium salt, or an anti-solvent.

Search terms in the WIPO IP Portal (142 results): CTR:WO AND PD:[01.01.2002 TO "\*"] AND IC\_EX:C08B37/00 AND (alga OR seaweed), where: CTR = Country; PD = Priority Date; IC\_EX = Exact IPC Code. https://patentscope.wipo.int/search/en/search.jsf. (accessed on 22 June 2022).

## 4.1. Supercritical CO<sub>2</sub> Extraction (CO<sub>2</sub>-SFE)

Studies performed with macroalgae as a raw material in CO<sub>2</sub>-SFE are of interest to those seeking to obtain antioxidant extracts (Table 4). They are relevant because this extraction method is a green alternative to petrochemical solvents (e.g., hexane) and is less energy- and time-consuming than distillation. Currently, a few studies have evaluated the use of macroalgae as renewable sources for CO<sub>2</sub>-SFE, mainly from brown species. Most of these studies showed the possibility of recovering antioxidants (e.g., carotenoids and phenolics) from the algal biomass and demonstrated that the use of co-solvents and high pressures ( $\geq$ 300 bar) and temperatures ( $\geq$ 50 °C) often favors better global extraction yield.

Table 4. Brief description of green extraction techniques.

Technology	Summary of the Technique	Ref
Supercritical CO <sub>2</sub> Extraction (CO <sub>2</sub> -SFE)	<ul> <li>It is an extraction method that uses CO<sub>2</sub>, a generally recognized as safe (GRAS) solvent, in its supercritical state (temperature over 31.1 °C and pressure over 74 bar). The addition of a co-solvent is a strategy that changes extraction polarity.</li> <li>While in the extraction process, the solvent flows continuously through the raw material, and an in-line step separates the extract from the solvent that recirculates in the system. When using multiple separators, the extract may be fractionated into fractions with different chemical compositions.</li> <li>The outputs of the process are solvent-free non-polar total extracts or fractions and an exhausted raw material that can be used in a downstream process. It is a zero-waste process.</li> </ul>	[72]
Pressurized Liquid Extraction (PLE)	<ul> <li>It is an extraction method that enables the use of solvents in a liquid state, even above their atmospheric boiling point. The process often ranges from room temperature to 200 °C and involves pressures between 3.5 and 20 Mpa.</li> <li>In this process, ethanol or an ethanol-water mixture can be used as a green solvent. Some works show that extraction efficiency may increase in a dual-solvent mixture. This happens because of the complementary effects of both solvents, i.e., while one improves the chemical compound's solubility, the other enhances its desorption from the raw material matrix.</li> <li>In the extraction process (dynamic or static), the solvent flows through the raw material to extract the chemical compounds of interest. Depending on the extraction temperature, the extract flows into a cooling unit to reduce temperature before collection.</li> </ul>	[73]
Subcritical Water Extraction (SWE)	<ul> <li>It is an extraction method that uses water in its subcritical state (temperature between 100 °C and 374 °C and pressure between 10 and 221 bar) as a solvent.</li> <li>In this process, when the water temperature (most important factor) and pressure increases, its polarity decreases. Additionally, subcritical water has better penetration into the raw material matrix due to its low viscosity and high diffusivity. In this manner, depending on extraction parameters, polar or non-polar compounds can be extracted.</li> <li>In the extraction process (dynamic or static), the solvent flows through the raw material to extract the chemical compounds of interest, with the hot extract then flowing into a cooling unit to reduce temperature before collection.</li> </ul>	[74]
Microwave-Assisted Extraction (MAE)	<ul> <li>It is an extraction method that enables the use of water and ethanol as a green solvent. Process temperature is a function of time and power (watts), and high pressure and temperature are associated with fast and efficient extraction. The extraction process can run in closed (sealed vessels) or opened systems that operate above or under atmospheric pressures, respectively.</li> <li>MAE in closed systems has the advantages of fast and efficient extraction and low solvent consumption. Its disadvantages include low biomass processing throughput, which is often associated with the loss of volatile compounds due to high pressure and temperature.</li> <li>MAE in opened systems has the advantages of fast extraction, high sample throughput, the possibility of using higher ratios of solvent/feed (associated with higher efficiency), and suitability for the extraction of thermolabile compounds. Its disadvantages include lower extraction efficiency and the higher oxidation of compounds compared to the closed system.</li> </ul>	[75–77]

Ktari et al. [78] compared the differences between solvent extraction (methanol) and  $CO_2$ -subcritical and  $CO_2$ -SFE extractions from the brown alga *Dictyopteris polypodioides* in terms of fucoxanthin (FX) and total phenolic (TP) content. This study showed that subcritical extraction (CO<sub>2</sub>-liquid at 25 °C, 400 bar) and CO<sub>2</sub>-SFE at mild temperatures (40 °C, 400 bar) had similar extraction yield and recovery of about 12% of FX. However, these conditions were more selective when extracting TP content (~2.2-fold higher than

methanol extraction). After increasing the temperature to 60 °C, the authors evaluated different pressures (300, 400, and 500 bar) that resulted in better FX recovery than the previous CO<sub>2</sub>-tested conditions, although recovery was lower than it was in methanol extraction (up to ~59%). Concerning TP content, the results at 60 °C were significantly higher than methanol extraction, and a pressure of 500 bar showed the best results for selectivity (~2.5-fold) and yield (~2-fold). It is interesting to notice that the CO<sub>2</sub>-liquid extraction (25 °C, 400 bar) of another brown alga, *Undaria pinnatifida*, showed better FX extraction selectivity than extraction at higher temperatures [79], an oppositive result to *D. polypodioides* even though they share matrix similarities (e.g., alginic acids and fucoidan).

In addition to using a myriad of extraction parameter combinations (e.g., pressure, temperature, solvent-to-feed ratio) to selectively extract some chemical classes, there is the strategy of employing co-solvents to modify the extraction fluid's polarity and density. Ospina et al. [80] investigated the effect of pressure (100, 200, and 300 bar), temperature (40, 50, and 60 °C), and co-solvent (2, 5, and 8% ethanol) on the extraction yield, antioxidant activity, and total carotenoid (TC) and TP content of the red alga Gracilaria mammillaris. In their study, the Pareto chart demonstrated that ethanol concentration and pressure were variables that positively correlated with TP content and extraction yield. In the case of TC content, the parameter pressure was the most relevant factor. Moreover, despite not being as efficient as the commercial antioxidants used as control (TBHQ, BHT, and gallic acid), the results demonstrated that all extracts had the capacity to protect against lipid peroxidation of the tested edible oil. Rozo et al. [81] showed comparable results for another red alga, Hypnea musciformis, using similar experimental conditions. In addition, they proved the presence of the antioxidant compounds phloretin and (-)-epicatechin, which are of great interest to the cosmetic industry. Saravana et al. [82] studied how the co-solvents sunflower oil (SFO), soybean oil, canola oil, ethanol, and water impact the extraction of TC, FX, and phlorotannins (PTs) from Saccharina japonica (Phaeophyceae). The results showed that 300 bar, 55 °C, and 2.0% co-solvent were the optimal conditions for achieving high TC, FX, and PT content for most modifiers. Among the co-solvents, water had the best performance for PTs, while SFO was more efficient in the recovery of TC and FX. The authors also showed that the strategy CO<sub>2</sub>-SFE + SFO yields rich fatty acid content, high antioxidant activity, and high oil stability.

#### 4.2. Pressurized Liquid Extracion (PLE)

PLE is another timesaving and solvent-reducing approach. It can work as a primary extraction technology and as a downstream process from other industrial techniques such as CO<sub>2</sub>-SFE [83]. Indeed, some works have demonstrated the feasibility of this strategy for renewable raw materials such as turmeric rhizome [84] and annatto seeds [85], showing the possibility of combining a biorefinery strategy with zero-waste practices because the "waste biomass" is a commercial-value carbohydrate-rich co-product. As a primary step or in a zero-waste biorefinery concept, PLE is a viable strategy for macroalgae biomass valorization (Table 4).

Fayad et al. [86] demonstrated that extracts obtained through green technologies from the brown macroalga *Padina pavonica* have anti-skin aging activity. In the PLE process, the authors mixed the biomass with diatomaceous earth (50:50 w/w) and ran two extraction cycles with water at 60 °C and 150 bar. The extract recovered from PLE inhibited 100% of hyaluronidase activity (HAase, EC 3.2.1.35) at concentrations similar to those of phlorotannin (polyphenolic) fractions from Eisenia bicyclis extracted with solvents, which is desirable for anti-aging activity [87]. Indeed, phenolic compounds are efficiently extracted through PLE, as demonstrated for the green macroalga Codium fragile [ethanol:water (80:20), 100 °C, and 68.9 bar] and the red macroalga Gracilaria gracilis [water, 120 °C, and 103 bar] [88]. However, other inexpensive technologies with generally recognized as safe (GRAS) solvents may retrieve better results than PLE, as demonstrated with *C. fragile*. In this case, it is pivotal to consider the efficiency and the scalability of the chosen technology in an economic feasibility evaluation. While solvent–liquid extraction of the

green macroalga had an extraction time of 24 h, the PLE extraction protocol was 25 min. Additionally, PLE is associated with low solvent use and, consequently, less time required to evaporate the solvent in downstream processes.

Another central aspect to consider is the global strategy of the industry. PLE is a multifunctional technology and a green alternative to organic solvents. Otero et al. [89] optimized two protocols to extract fatty acids from the brown alga Laminaria ochroleuca. By using ethanol at 120 °C and 100 bar, the extraction favored the presence of unsaturated fatty acids (USFAs) over saturated fatty acids (SFAs), i.e., USFA/SFA was 1.24. Otherwise, running PLE with ethanol:water (2:1) at 120 °C and 100 bar yielded an extract with a higher proportion of SFAs, i.e., USFA/SFA was 0.79. Even though the first protocol favored USFA extraction, the global extraction yield was about three-times lower than the ethanol:water extraction. Therefore, the absolute content of USFA yield was higher with the second protocol (USFAs per dw) by about 2.26-fold. By applying one of the well-known downstream protocols for USFA and SFA separation [90], ethanol:water extraction favors the best use of the algal biomass.

Moreover, some studies have demonstrated the technical feasibility of using PLE to extract polysaccharides (PS). Dobrincic et al. [91] tested the efficiency of PLE on the waste biomass (a by-product from solvent extraction) of the brown algae Gongolaria barbata (formerly Cystoseira barbata) and Fucus virsoides and compared the results with other technologies. The optimized extraction parameters were 0.1 M H<sub>2</sub>SO<sub>4</sub> for two cycles of 15 min at 105 °C and 103 bar with a downstream process for PS precipitation. Compared to conventional extraction, PLE reduced solvent usage and extraction time (from 3 h to 30 min) while having similar or higher PS content for G. barbata and F. virsoides. In addition, PS had a higher proportion of sulfate groups in both algae. In another study, Diop et al. [92] showed the technical feasibility of an upcycling approach by extracting agar from the red alga Gelidium corneum (formerly Gelidium sesquipedale), which was collected from the waste stream of a primary industrial phycocolloid extraction. In this study, agar recovery and its physicochemical characteristics were ideal in PLE with water at 100 °C and 10.13 bar. Additionally, the authors demonstrated that the different temperatures, pressures, algae-to-water ratios, and extraction times tested affected gel strength, hysteresis, hardness, cohesiveness, gumminess, adhesiveness, and springiness.

#### 4.3. Subcritical Water Extraction

Subcritical water extraction (SWE) is a modern technique that uses temperature variations to selectively extract polar and non-polar compounds from raw materials [93]. This allows subcritical water to carry out selective extractions, such as the extraction of polar compounds at lower temperatures and less polar compounds at higher temperatures, which is useful for both the extraction and hydrolysis of proteins and other fractions (lipids, carbohydrates, phenolics). However, proper selection of operating conditions is necessary to maximize extraction yield and avoid degradation to monomer units and decomposition products [94].

Pangestuti et al. [95] used this technique to hydrolyze *Hypena musciformis* (Rhodophyta) and obtain antioxidants. Thus, a material with good antioxidant activity can be recovered at 210 °C, with sugar and emulsion formation at <180 °C also observed, which demonstrates the possibility of using this process and macroalga for more of a cosmetic application. Furthermore, *Caulerpa acemosa* (sea grapes) and *Ulva lactuca* (sea lettuce) (Chlorophyta) were submitted to SCWE and analyzed for their nutritional values and the recovery of bioactive compounds. From there, a significantly higher extraction yield was seen with this technique, which also provided higher protein and sugar content; greater total phenolic content (TPC), total saponin content (TSC), and total flavonoid content (TFC); and improved antioxidant activity. Cytotoxic assays also revealed that the hydrolysates of these macroalgae did not show any toxic effect on monocyte/macrophage-like cells at certain concentrations, suggesting that hydrolysates are both safe and non-toxic for applications in food, cosmeceuticals, and nutraceuticals.

Interestingly, Flórez-Fernández and Domínguez [96] decided to use this method to extract alginate, fucose-rich sulfated polysaccharides and phlorotannins from *Sargassum* sp. They noticed that the valorization of the alginate fraction obtained was more efficient in relation to the biorefinery concept applied to this macroalga in the production of components with interesting biological properties. Additionally, other studies [97] involved this method to obtain greater energy efficiency in several stages of the process of a biorefinery, as well as to obtain biomolecules of interest during scaled production.

## 4.4. Microwave-Assisted Extracition (MAE)

Microwave-assisted extraction (MAE) is a technique that occurs as a result of changes in cell structure that are caused by electromagnetic waves. Using microwaves to heat solvents and plant tissues increases extraction kinetics, and several advantages are gained over traditional solvent extraction, including shorter extraction times, higher extraction rates, lower costs, less solvent use, moderately high recoveries, and minimal sample preparation [98]. As shown in Table 5, sulfated polysaccharides (fucoidan) from the brown seaweed Ascophyllum nodosum were extracted using this technology, and the optimal yield of this polysaccharide was 16.08%; from extraction at 120 °C for 15 min, all fucoidans exhibited antioxidant activities as measured by the elimination and reduction of DPPH, among which the fucoidan extracted at 90 °C exhibited the highest degree of activity [99]. This study shows that MAE is an efficient technology for the extraction of sulfated polysaccharides from seaweed, and *Ascophyllum nodosum* can potentially be a resource for natural antioxidants. It is also worth mentioning that this same method extracted considerable yields of carrageenan from *Hypnea musciformis* during MAE, and the hybrid kappa/iota carrageenan obtained by this method was comparable to that extracted by the conventional technique [100]. This reveals that macroalgae can be scanned for as many applications as possible in the same product.

Technology	Species of Seaweed, Color	Highlights	Reference
Supercritical CO <sub>2</sub> Extraction (CO <sub>2</sub> -SFE)	Dictyopteris polypodioides, brown	The extraction with $CO_2$ at 60 °C resulted in higher global extraction yield and fucoxanthin content than lower temperatures but was not affected by the tested pressures. Total phenolic content and DPPH antiradical scavenging capacity results showed the same behavior.	[78]
	Gracilaria mammillaris, red	The extraction operated with $CO_2$ + ethanol (as a co-solvent). The co-solvent concentration and pressure positively correlated with global extraction yield and the concentration of total phenolics extracted, while pressure was the most relevant factor for total carotenoid (TC) content. The extracts reduced the lipid oxidation of the tested edible oil, although they were not as effective as the reference antioxidants.	[80]
	Hypnea musciformis, red	Different conditions of extraction with CO <sub>2</sub> resulted in extracts with antioxidant activities, and the proportion of ethanol (co-solvent) directly correlated with the increase in antioxidant activity (ABTS) and protection against lipid peroxidation. Phloretin and (-)-epicatechin were the phenolics found in the study.	[81]
	Saccharina japonica, brown	The use of $CO_2$ + sunflower oil (as co-solvent) favored the extraction of total carotenoids and fucoxanthin, the yield of fatty acids, high antioxidant activity, and high oil stability; $CO_2$ + water (as co-solvent) was more efficient for the extraction of phlorotannins.	[82]

Table 5. Production of sustainable ingredients from some macroalgae through green technologies.

Technology	Species of Seaweed, Color	Highlights	Reference
	<i>Undaria</i> pinnatifida, brown	The use of $CO_2$ extraction recovered fucoxanthin from seaweeds discharged into the environment due to non-adherence to food quality standards. In subcritical conditions (400 bar, 25 °C), the extraction was more selective, while supercritical conditions favored high fucoxanthin recovery.	[79]
Pressurized Liquid Extraction (PLE)	<i>Codium fragile,</i> green	The extraction with ethanol:water (80:20) at 100 °C and 68.9 bar was more selective in the recovery of TP than other solvents tested with PLE, despite having lower extraction yield than the protocol with water at 100 °C and 103 bar. Additionally, the extracts had higher antioxidant activity. However, most PLE protocols had lower performance than solid–liquid extraction (SLE).	[88]
	Gongolaria barbata, brown	Pre-treatment of the raw material included seaweed maceration with (1st step) acetone (18 h, at room temperature) and (2nd step) ethanol (4 h, at 70 °C). Distilled water and $H_2SO_4$ were the solvents tested at a constant pressure under different temperatures to extract polysaccharides (PS). The optimized protocol reduced the extraction time to 30 min (3 h for conventional extraction) and resulted in similar PS extraction yield. Furthermore, PS presented higher sulfate group proportions and lower uronic acid content than PS from conventional extraction, although with lower antioxidant activity.	[91]
	Fucus virsoides, brown	Pre-treatment of the raw material included seaweed maceration with (1st step) acetone (18 h, at room temperature) and (2nd step) ethanol (4 h, at 70 °C). Distilled water and $H_2SO_4$ were the solvents tested at a constant pressure under different temperatures to extract PS. The optimized protocol reduced the extraction time to 30 min (3 h for conventional extraction) with a higher PS extraction yield. Likewise, the PS had higher sulfate group proportions and fucose content alongside lower uronic acid content and antioxidant activity than PS from conventional extraction.	[91]
	Gelidium corneum, red	In an upcycling approach (algae from a waste stream of a primary industrial phycocolloid extraction), agar extraction was possible with water at 100 °C and 10.13 bar. It showed that the different temperatures, pressures, algae-to-water ratios, and extraction times tested affected gel strength, hysteresis, hardness, cohesiveness, gumminess, adhesiveness, and springiness.	[92]
	<i>Gracilaria gracilis,</i> red	Extraction with water at 120 °C and 103 bar was the protocol with the highest extraction yield. Statistically, there was no difference among the protocols tested for PLE regarding TP content, DPPH scavenging activity, and antioxidant activity. The extraction yield of PLE with water was similar to most SLE protocols, though the extract presented lower TP recovery, DPPH scavenging activity, and antioxidant activity.	[88]
	Laminaria ochroleuca, rown	The use of ethanol at 120 °C and 100 bar was the optimized protocol that favored the extraction of unsaturated fatty acids (USFAs), while ethanol:water (2:1) favored the extraction of saturated fatty acids (SFAs). However, the absolute content of USFAs was ~2.26-fold superior with ethanol:water because of the higher global extraction yield (~3-fold) than ethanol. In addition, ethanol:water was more efficient at recovering TP content.	[89]
	Padina pavonica, brown	The optimum extraction condition was two extraction cycles with water at 60 $^{\circ}$ C and 150 bar, in which the extract inhibited 100% of hyaluronidase activity.	[86]

Table 5. Cont.

Technology	Species of Seaweed, Color	Highlights	Reference
Subcritical Water Extraction (SWE)	Caulerpa racemosa, green	Processes tested at different temperatures (110 to 230 °C with 40 °C increments) and 50 to 70 bar yielded up to ~60% (dw basis) acidic hydrolysate. Regarding global yield, 190 °C was the optimal temperature. At 230 °C, the extract had stronger ultraviolet B (UVB) absorption, higher total protein content, higher TP content, higher total flavonoid (TF) content, higher total saponin (TS) content, and greater antioxidant activity.	[18]
	Codium tomentosum, green	The multi-step isobaric process (100 bar, temperature range of 20 to 250 °C) yields up to 51.4% cumulative extract. The increase in temperature augmented TP and TF content, but phlorotannin content was higher at low temperatures. It is noteworthy that free amino groups positively correlate to higher temperatures and that reducing sugar content increased compared to the raw material, indicating the presence of hydrolysis.	[70]
	Hypnea musciformis, red	Hydrolysis efficiency ranged from 61.37 to 81.23% at the different solvent-to-feed (S/F) ratios (50:1, 100:1, and 150:1) and temperatures (120 to 270 °C with 30 °C increments) that yielded acidic extracts. Regarding global yield, the tested temperatures over 210 °C showed higher hydrolysis efficiencies and were not affected by the S/F ratio tested. The combination of 210 °C and an S/F ratio of 50:1 was the optimal condition for obtaining high total protein, high TP, and high TF content, which positively correlated with the evaluated antioxidant activity.	[95]
	Saccharina japonica, brown	The input raw material for the tests was a CO <sub>2</sub> supercritical de-oiled seaweed, and SWE was an upstream step for alginate and fucoidan extraction. The procedures ran at different temperatures (100, 125, and 150 °C), pressures (10, 30, and 50 bar), deep eutectic solvent mixtures with water (30, 40, and 50%), and S/F ratios (30:1, 40:1, and 50:1). According to the statistical model, the optimal parameter combination was 150 °C, 19.85 bar, 30% choline chloride:glycerol (1:2) in water, and an S/F ratio of 36.81:1, which yielded 28.12% and 14.93% functional alginate and fucoidan, respectively. However, they presented lower antioxidant activity when compared to commercial standards.	[101]
	Sargassum thunbergii, brown	The processes tested at different temperatures (120 to 240 °C with 30 °C increments) at an isobaric pressure of 30 bar and with an S/F ratio of 20:1 reached up to ~80% extraction efficiency (EE). A temperature of 180 °C presented relevant EE (70.33%), and the maximum values observed for total phlorotannins positively correlated with the antioxidant activity tested. Additionally, some phenolic compound concentrations were evaluated and ranked as follows: pyrogallol > p-coumaric acid > chlorogenic acid = protocatechuic acid > gallic acid > syringic acid.	[102]
	<i>Ulva lactuca,</i> green	Processes tested at different temperatures (110 to 230 °C with 40 °C increments) and at 50 to 70 bar yielded up to ~45% (dw basis) acidic hydrolysate. Regarding global yield, 190 °C was the optimal temperature. At 230 °C, the extract had higher total protein, higher TP, higher TF, and higher TS content and greater antioxidant activity. UVB absorption was strong and similar for extracts obtained at 190 and 230 °C.	[18]

Table 5. Cont.

Technology	Species of Seaweed, Color	Highlights	Reference
Microwave-Assisted Extraction (MAE)	<i>Gongolaria</i> <i>barbata,</i> brown	Pre-treatment of the raw material included seaweed maceration with (1st step) acetone (18 h, at room temperature) and (2nd step) ethanol (4 h, at 70 °C). Distilled water, 0.1 M HCl, and 0.1 M H <sub>2</sub> SO <sub>4</sub> were the solvents tested (S/F 30:1) at different temperatures (60, 80, and 100 °C) and with different extractions times (10, 20, and 30 min) for the extraction of polysaccharides (PS). The optimized protocol (0.1 M H <sub>2</sub> SO <sub>4</sub> at 80 °C) reduced extraction time to 10 min [3 h for conventional extraction (CE)] and yielded ~15% PS. The PS had a higher sulfate group proportion and lower uronic acid content than PS extracted with CE. In addition, the extract had higher antioxidant capacity, though radical scavenging capacity was lower than that of CE.	[91]
	Fucus virsoides, brown	Pre-treatment of the raw material included seaweed maceration with (1st step) acetone (18 h, at room temperature) and (2nd step) ethanol (4 h, at 70 °C). Distilled water, 0.1 M HCl, and 0.1 M H <sub>2</sub> SO <sub>4</sub> were the solvents tested (S/F 30:1) at different temperatures (60, 80, and 100 °C) and with different extractions times (10, 20, and 30 min.) for the extraction of polysaccharides (PS). The optimized protocol (0.1 M H <sub>2</sub> SO <sub>4</sub> at 80 °C) reduced extraction time to 10 min [3 h for conventional extraction (CE)] and yielded ~20% PS. The PS had a higher sulfate group proportion and lower uronic acid content than PS extracted with CE. In addition, the extract had higher antioxidant capacity and a similar radical scavenging capacity to CE.	[91]
	<i>Gelidium amansii,</i> red	MAE was the first step in producing cellulose microfibrils. Distilled water, 1% NaOH, and 1% $H_2SO_4$ were the solvents tested (S/F 10:1) at different temperatures (100 to 180 °C) in the exploration of conditions that favor cellulose extraction over agar. The optimized protocol was the use of distilled water for 10 min at 180 °C. The derived cellulose microfibrils exhibited anti-inflammatory activity. Additionally, this material might be employed as an active functional nanomaterial for cosmetics.	[103]
	Padina pavonica, brown	The optimum extraction condition was the use of water at 60 $^{\circ}$ C and with 1000 watts, in which the extract inhibited 100% of hyaluronidase activity.	[86]
	Sargassum swartzii, brown	The combination of different ethanol concentrations (20 to 96% with 20 °C increments), S/F ratios (15:1 to 40:1 with 5:1 increments), microwave power (80 to 720 W with 160 W increments), and extractions times (15 to 90 min with 15 min increments) yielded phlorotannin extracts with antioxidant activity. The optimized protocol determined by a statistical model had the following parameters: 65 min, ethanol 52%, microwave power 613 W, and S/F ratio 33:1.	
	<i>Ulva lactuca,</i> green	Extraction with 70% ethanol at 90 °C (1500 W) with an S/F ratio of 15:1 for 30 min resulted in a yield of ~22% of an extract with significant TP content and antioxidant activity. The dermo-cosmetic preparations (a gel and an emulsion) made with the extract were thermally and mechanically stable. Additionally, these formulations were efficient in the active skin permeation and cutaneous retention test.	[104]

Table 5. Cont.

Technology	Species of Seaweed, Color	Highlights	Reference
	<i>Ulva australis</i> (formerly <i>Ulva</i> <i>pertusa),</i> green	Pre-treatment of the raw material consisted of seaweed maceration (S/F 4:1) with 80% ethanol (2 h, at 85 °C) for pigment removal, followed by centrifugation and drying. Distilled water was the solvent used for the tests with different extraction times (30, 45, and 60 min), power (500, 600, and 700 W), S/F ratios (40:1, 55:1, and 70:1), and pH levels (5, 6, and 7), which yielded up to ~41% of an ulvan extract that showed antioxidant activity. Additionally, it upregulated the expression and enhanced the activity of the antioxidant enzymes superoxide dismutase and catalase. The optimized protocol parameters were the following: distilled water, ~44 min, 600 W, S/F ratio of 55.45, and a pH of 6.57.	[105]

Table 5. Cont.

## 5. Safety of Algae in Cosmetics

Before reaching the shelves, the safety of these products based on algae must be effectively assessed. Not only the safety of the consumer, but also the safety of the environment that will be impacted by these products of algal origin must be considered. This issue relates to current legislation regarding production and preparation.

Due to the growth of the industry, a quality control process for safety and effectiveness is necessary to prevent the occurrence of scandals such as the Morhange talcum powder scandal of 1973. Deaths resulted from the presence of hexachlorophene in Morhange's talcum powder (hexachlorophene is a potent bactericide at excessive levels). The French government reacted immediately and withdrew all boxes of talcum powder from the market. At the time, the toxicity of hexachlorophene was not known to the general public. An unpublished study of guinea pigs in 1939 showed that about ten of them died three days after ingestion of the product [106]. At the time, the product did not present any particular hazard in its nominal composition. The company Morhange, which marketed the product, had neither the equipment nor the competent personnel to carry out compliance checks, with the packaging company also lacking such resources. Legislation did not initially classify hexachlorophene as a dangerous substance, a deficiency that was remedied in September 1972 and September 1973 [8]. The case of Lush Lure in 1933 is also worth mentioning, as their mascara promised women that they could achieve the permanent appearance of eyelashes with aniline dye. Regrettably, some women were subsequently blinded due to the presence of the chemical p-phenylenediamine. This incident was directly linked to the passage of the 1938 Food, Drug, and Cosmetic Act in the United States of America, which was introduced by the Food and Drug Administration (FDA) after the need for more regulation was revealed [107]. These examples and a few others forced health legislation around the world to more seriously focus on cosmetics, including consideration of key concepts and differences and consumer requirements.

When thinking about plans to better develop policies to deal with this development of safe products, even in terms of products of algal and natural origin that arise through the increase in conscious consumer demand, one must consider the presence of various international organizations and their guidelines (Table 6).

From a cosmetics perspective, the OECD makes testing guidelines which are covered by the OECD Mutual Acceptance of Data (MAD) system and that show the results of laboratory tests related to the safety of chemicals that are generated following these guidelines and the OECD Principles of Good Laboratory Practice. These standards are accepted in all OECD and acceding countries for safety assessment and other uses related to the protection of human health and the environment [108], and some examples can be seen in Table 7.

#### Table 6. Definition of international bodies of standardization.

## Definition of International Bodies of Standardization

About OECD

"The Organization for Economic Co-operation and Development is an international organization that works to build better policy together with governments and citizens, thus setting evidence-based international standards and finding solutions to a range of social, economic, and environmental challenges."

About ISO "International Organization for Standardization is an independent, non-governmental international organization with a membership of 167 national standards bodies. Through its members, it brings together experts to share knowledge and develop voluntary, consensus-based, market relevant International Standards that support innovation and provide solutions to global challenges."

About SCCS

"The Scientific Committee on Consumer Safetyprovides Opinions on health and safety risks (chemical, biological, mechanical and other physical risks) of non-food consumer products (e.g., cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products) and services (e.g., tattooing, artificial sun tanning)."

**Table 7.** Some examples of mandatory tests to be conducted according to the OECD or ISO guidelines for cosmetics.

Guide	Briefing Description
ISO 10993-5 (Test for in vitro cytotoxicity)	It describes methods for assessing cytotoxicity in vitro and specifies the incubation of cultured cells in contact with a device and/or extracts from a device directly or by diffusion. These methods are designed to determine the biological response of mammalian cells in vitro using appropriate biological parameters.
OECD 432 (Test of photocytotoxicity)	It describes an in vitro method for the evaluation of photocytotoxicity via relative reductions in the viability of cells exposed to the chemical in the presence versus absence of light.
OECD 439 and ISO 10993-10 (Skin irritation test)	They describe in vitro procedures that can be used for hazard identification in irritating chemicals (substances and mixtures) following Category 2 of the UN Globally Harmonized System of Classification and Labeling of Chemicals (GHS). The methods are based on the reconstructed human epidermis (RhE), which in its overall design closely mimics the biochemical and physiological properties of the upper parts of human skin and offers key factors for the interpretation of results.
OECD 431 (Test of cutaneous corrosivity)	This method allows for the identification of corrosive chemical substances and mixtures, as well as the identification of non-corrosive substances and mixtures when supported by a weight of evidence determination using other existing information. The test protocol can also indicate the distinction between severe and less severe skin corrosives. This test guideline does not require the use of live animals or animal tissue for the assessment of skin corrosivity.
OECD 491 (Test of eye irritation/corrosivity)	It describes an in vitro cytotoxicity-based assay that is performed on a confluent monolayer of Statens Seruminstitut Rabbit Cornea (SIRC) cells cultured on a 96-well polycarbonate microplate.
OECD 428 (Test of skin permeation/absorption)	This method provides information on the absorption of a test substance (preferably radiolabelled) applied to the surface of a skin sample that separates the two chambers (a donor chamber and a recipient chamber) of a diffusion cell. Static and flow diffusion cells are both acceptable. Human or animal skin can be used.
OECD 129 (Test for prediction of oral toxicity)	This method is an in vitro alternative to animal testing that estimates starting doses for oral systemic toxicity tests.
OECD 442E (Test of skin sensitization)	The present key event-based test guideline (TG) addresses the human health hazard endpoint of skin sensitization following exposure to a test chemical. Skin sensitization refers to an allergic response following skin contact with the tested chemical, as defined by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS).
OECD 487 (Test of genotoxicity)	The assay detects the activity of clastogenic and aneugenic test substances in cells that have undergone cell division during or after exposure to the test substance. It is an in vitro micronucleus test for the detection of micronuclei in the cytoplasm of interphase cells.

In addition to the OECD there is also the ISO, and its main function in conjunction with the technical committees is to prepare international standards. For cosmetics, some guidelines are intended to guide good manufacturing practices for these products, specifically ISO 22716:2007 and ISO 16128-1. ISO 22716:2007 guides documentation and regulation of the production, control, storage, and shipping of cosmetic products, without forgetting to demand excellent levels of quality management. According to ISO 16128-1, to be classified as natural, the product must contain natural ingredients. For organic certification, a minimum percentage of ingredients from organic production is required, and [109] marine macroalgae in this environment are progressively occupying the place that botanical ingredients have long occupied, with great diversity across multiple categories.

When it comes to algae in this environment, the European Union has the SCCS and its guidance notes for the testing of cosmetic ingredients and safety assessment (NoG). The most recent was the one adopted in March 2021, where, to use algae in cosmetic products, common or usual names, variety names, species, genus, and family information are recommended if more than one variety of species from a given source is used. Each species must be specified through organoleptic, macroscopic, and microscopic assessment, with morphological and anatomical description (including genus, if applicable) and a photograph of the alga or part of the alga also required. The natural habitat, geographic distribution, and current sources of the alga, including its geographic location and whether it is cultivated or harvested in nature, is also required. Further, a description of the preparation process (harvesting, washing, drying, extraction, distillation, destructive distillation, eventual purification, conservation procedures), handling, transport, storage, and the commercial form is necessary, including whether the algae are used in the form of a powder, solution, or suspension. Characteristic elements of the composition should also be declared (identification of characteristic components, known toxic components (%), physical specifications, chemical and microbiological quality including relevant fungi, additional external contamination, preservatives and/or other additives added). Therefore, it is not a simple process and requires several tests for this macroalgae-based product to reach market shelves.

Furthermore, there is also the presence of Safety Data Sheets (SDS), which disclose a list of hazardous ingredients in a product, their physical and chemical characteristics, their effect on humans, the associated physical and environmental health hazards, the chemicals with which they may react adversely, precautions to take when handling, the types of measures that can be used for exposure control, emergency and first aid procedures, methods of containing a spill, and safety precautions for handling, storing, and transporting the chemical. SDSs are required to be presented in a consistent, user-friendly, 16-section format to help workers who handle hazardous chemicals to become familiar with the format and understand the contents of the datasheets. This is necessary as each hazard rating needs to be considered in the safety assessment of cosmetic ingredients, particularly when using algae extracts in the product. Here, once again, the importance of choosing the appropriate extraction technology and the best characterization of that extract and its effects is highlighted. Though a natural product, the use of macroalgae and the process of obtaining it is still biotechnological and must therefore also go through verification steps and safety checks.

When pondering about environmental safety related to extracts obtained from macroalgae, it should be considered that even the solvent selection stage can lead to greater environmental impacts due to the use of solvents derived from fossils and toxics, even though these are more economical. Tanzi et al. [110] have already identified a green solution to replace hexane in this type of extraction, which was the use of terpenes (limonene, pinene, cymene) obtained from renewable raw materials that act as alternative solvents while obtaining similar lipid extraction yields to those obtained with hexane. Thus, here comes the bottom line of the matter: it is not only reduced solvent use that can be considered "green", but also the choice of which solvent will be used, as this becomes part of the development and sustainability of production. It is worth noting that MSDSs also have a mandatory section in their reports on ecological information that assesses the environmental impact of the chemical(s) if released into the environment, which is Section 12 of this report. In addition, Section 13 concerns disposal considerations and guidance on proper disposal practices, recycling or recovery of the chemical(s) or its container, and safe handling practices. Therefore, all this is necessary to reach the ideal level of suitability, since the extracts obtained through algae, despite being advantageous in several applications, must be safe. As such, these tests must be carried out.

Related to safety, the mandatory toxicological tests of this seaweed extract are also preceded by pre-clinical tests, which is indicated by the Scientific Committee on Consumer Safety (SCCS). These tests assess acute systemic toxicity, dermal corrosivity and irritation, skin sensitization, skin absorption/penetration, the toxicity of repeated doses, mutagenicity/genotoxicity, subacute and subchronic toxicity, eye irritation, mucosal irritation, UV radiation-induced toxic effects (phototoxicity, genotoxicity, photoallergy), carcinogenicity, developmental and reproductive toxicity (teratogenicity), toxicokinetics, and toxicodynamics. Each test mentioned above is based on an OECD guideline, such as skin irritation, which corresponds to OECD 404. All this is necessary to reach the ideal level of adequacy.

It is worth mentioning the evolution of animal-free tests, which, in a way, involve the aspect of technological evolution and which are certainly included in this "green wave" provided by consumer appeal, such as the search for the insertion of natural products. There are alternative methods that, according to Cruelty Free International, are a good substitute for tests on animals, such as in vitro human cell and tissue culture, the use of computer models, and even the use of human volunteers. One of these alternatives is the use of skin models, not only because it is physiologically relevant in drug development, but also because it provides a better prediction of human skin safety alongside advantages concerning ethical issues and economic factors. The use of reconstructed human skin (RHS) is a way to detect the potential for phototoxicity without testing on animals, and studies such as that by Tavares et al. [111] have used this method to evaluate the photoprotective potential of a molecule and its formulation in sunscreen.

This type of RHS and 3D tissue construct is a logical follow-up tool to standard '2D' genotoxicity assays as it supports more natural cell–cell and cell–matrix interactions and shows 'life-like' behavior related to key parameters such as cell proliferation and gene expression [112]. This makes this alternative essential for cosmetology testing and OECD guidelines such as 431 (Reconstructed Human Epidermis Test Method (RHE)). Consequently, emerging cosmetics markets require the use of human cell-based testing systems. In parallel, studies have proven the applicability of new organ-on-chip compatible RHS for the assessment of substance effects [111], which reveals the increasing amount of studies into 3D fabrics and their technological development.

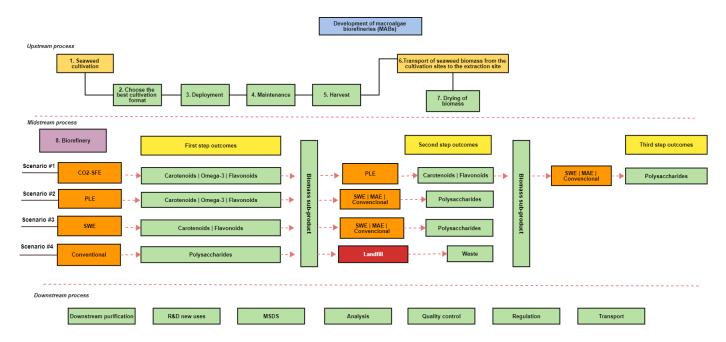
## 6. Industrial Perspectives in a Macroalgae Biorefinery Concept and Its Social and Environmental Impact

Macroalgae have different cultivation methods that vary depending on location and algae species. Examples of cultivation methods include raft, rope, tube-net, bag-net, long-line, monocline, bag, tank, and photobioreactor cultivation. In more complex cultivation systems, macroalgae have been evaluated as biofilters in Integrated Multi-Trophic Aquaculture (IMTA) because of their basal trophic level. Recently, Carneiro et al. [113] showed that IMTA of shrimp (*Litopenaeus vannamei*) and the red alga *Gracilariopsis tenuifrons* resulted in biomass increases in macroalga (up to one week of cultivation) and shrimp. In this sense, the production for industrial purposes of high-quality seaweed biomass with minimal nutrient requirements for sustainable cultivation on land is increasingly encouraged [114].

A supply chain that starts with the source of macroalgae biomass (harvested or cultivated) and passes through industrial processes to end up with the final products is of great interest to the bioeconomy and blue economy. When considering the consumption of the final products in a circular regenerative economy such as cosmetics, macroalgae

biorefineries (MABs) are pivotal in reducing the carbon footprint. For example, in a cradleto-cradle simulation, Seghetta et al. [115] evidenced that converting 100% of macroalga biomass into a protein-rich fish feed, a liquid fertilizer, and ethanol resulted in a net reduction in atmospheric  $CO_2$ . In this simulation, macroalgae cultivation and soil's carbon retention were the key players in carbon footprint mitigation. Therefore, MABs emerge as a solution for improving macroalgae biomass use in a zero-waste concept.

According to Saral et al. [116], the biorefinery is a framework or structure in which biomass is optimally used to produce multiple products with the aim of being self-sustainable and not harmful to the environment. In this sense, the use of green technologies (see Table 5) is of great interest. An illustrative scenario of an integrated MAB based on the combination of the aforementioned green technologies (CO<sub>2</sub>-SFE, PLE, SWE, and MAE) is shown in Figure 7.



**Figure 7.** Illustrative scenarios of integrated biorefineries involving macroalgae biomass processing with green technologies.

As a first step,  $CO_2$ -SFE is a substitute for a petrochemical solvent (e.g., hexane) that can be used to recover non-polar ingredients. It is a technology that operates at mild temperatures and that can fractionate volatile and heavy components. Since it is a versatile technique, the extraction may be performed with  $CO_2$  to yield solvent-free extracts or can be conducted using co-solvents as polarity modifiers (e.g., ethanol, vegetal oils, and water). Since all solvents are GRAS and there is no hazardous residual, the waste biomass becomes a sub-product for downstream processes. As demonstrated for the brown macroalgae D. polypodioides and U. pinnatifida (Table 5), CO<sub>2</sub>-SFE effectively recovers antioxidant extracts containing the carotenoid fucoxanthin. When using co-solvents (ethanol or water) to reduce extraction polarity, the process favors the presence of total carotenoids and phenolics in extracts. By using ethanol, the cosmetic high-value bioactive compounds phloretin and (–)-epicatechin were recovered from the red macroalga H. musciformis (Table 5). In addition, fatty acids, such as long-chain omega-3, were extracted from the brown macroalga S. japonica using sunflower oil as a co-solvent (Table 5). Once pure supercritical CO<sub>2</sub> extracts non-polar chemicals, high-value ingredients remain in the sub-product biomass. In this sense, a sequential process involving PLE to recover these compounds may be an efficient strategy, as demonstrated for other renewable raw materials such as turmeric [84]. The macroalgae C. fragile, G. gracilis, L. ochroleuca, and P. pavonica (Table 5) have compounds that can be extracted by PLE, such as PUFAs, pigments, and phenolic compounds. For

the cosmetic industry, these ingredients may enable their final products to claim antiinflammatory, anti-aging, antipollution, and photoprotective properties. As the last step in the MAB process., SWE, MAE, and conventional extractions shall be the chosen techniques for extracting polysaccharides (PS) from PLE biomass sub-products. Indeed, Dobrincic et al. [91] and Saravana et al. [101] demonstrated the technical feasibility of using MAE and SWE to extract functional PS from de-oiled brown macroalgae (Table 5).

All the mentioned MAB processes seek to upcycle the macroalgae biomass in the zerowaste practice that favors the circular regenerative economy and blue economy, allowing the macroalgae supply chain to attend to most of the 17 Sustainable Development Goals (SDGs) of the United Nations (Table 8). This illustrates that innovative MABs can contribute to climate change mitigation, local partnership promotion, and gender equality, among other social and economic benefits.

**Table 8.** Definition of the Sustainable Development Goals (SDGs) of the United Nations (UN) (United Nations, 2022) and how MABs can contribute according to UN targets and indicators.

SDGs	MABs Contribution
SDG 1: No Poverty: "End poverty in all its forms everywhere."	MABs contribution: Responsible harvesting and cultivation of macroalgae may contribute to incomes > USD 1.25 per capita per day.
SDG 2: Zero Hunger: "End hunger, achieve food security and improved nutrition and promote sustainable agriculture."	MABs contribution: Indirect enhancement to productivity in macroalgae farming. An MAB transforms 100% of biomass into products, making less biomass necessary. Additionally, the price of raw materials increases in a Fairtrade business model, expanding farmers' incomes.
SDG 3: Good Health and Well-Being: "Ensure healthy lives and promote well-being for all at all ages."	MABs contribution: Macroalgae are a source of bioactive compounds against neglected tropical diseases.
SDG 4: Quality Education: "Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all."	MABs contribution: From macroalgae harvesting or cultivation until extraction with green technologies, MABs need qualified technical professionals. In a couple of years, women and men can develop the skills required for a new sustainable industry.
SDG 5: Gender Equality: "Achieve gender equality and empower all women and girls."	MABs contribution: All businesses aware to stakeholder interests must implement corporate governance, in which a guideline addresses different day-to-day aspects in a company, including gender equality practices.
SDG 6: Clear Water and Sanitation: "Ensure availability and sustainable management of water and sanitation for all."	MABs contribution: In an IMTA alongside macroalgae, the reduction in eutrophication is proven.
SDG 7: Afford Clean Energy: "Ensure access to affordable, reliable, sustainable and modern energy for all."	Macroalgae contribution: Macroalgae can remediate polluted areas, e.g., areas contaminated with heavy metals. This biomass cannot be a raw material for an MAB but is useful for energy production.
SDG 8: Decent Work and Economic Growth: "Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all."	MABs contribution: Green technologies have high productivity and add value to commodities locally. This favors the development of local technological industries and mitigates the carbon footprint resulting from overseas/road transportation of raw material commodities.
SDG 9: Industry, Innovation, and Infrastructure: "Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation."	MABs contribution: MABs can be highly technological, lean, and small-scale while also having the capability to increase the local gross domestic product.
SDG 10: Reduce Inequalities: "Reduce inequality within and among countries."	MABs contribution: Increase in income per capita through a Fairtrade relationship. Local MABs may foster the replication of business models such as that of the Association of Seaweed Farming in northeast Brazil, in which women are the key players in the sustainable harvesting and cultivation of macroalgae and the sale of goods made of macroalgae.

## Table 8. Cont.

SDGs	MABs Contribution
SDG 11: Sustainable Cities and Communities: "Make cities and human settlements inclusive, safe, resilient and sustainable."	MABs contribution: As a cultural and natural heritage, macroalgae harvesting traces its origins to ancient fishing traditions. Local MABs must allocate part of their profits to recover and preserve natural macroalgae beds as a long-term strategy for raw material supply.
SDG 12: Responsible Consumption and Production: "Ensure sustainable consumption and production patterns."	MABs contribution: The supply chain is sustainable. When macroalgae origin is an IMTA, MABs promote lower water footprint and reduce eutrophication issues related to other commercial goods.
SDG 13: Climate Action: "Take urgent action to combat climate change and its impacts."	MABs contribution: In a circular regenerative economy, MABs are pivotal in reducing the carbon footprint.
SDG 14: Life Below Water: "Conserve and sustainably use the oceans, seas and marine resources for sustainable development."	MABs contribution: MABs reduce eutrophication and water and carbon footprints. With the implementation of a sustainable harvesting strategy, macroalgae provide shelter and food for ocean-living organisms. Aside from the MAB, macroalgae bioremediates polluted areas, and these biomasses can serve as raw material for energy production.

## 7. Conclusions

Here, we demonstrated how MABs with green technologies maximize renewable macroalgae biomass use, yielding high-value ingredients for the cosmetic industry. In addition, beyond the technical viability of obtaining different potential cosmetic ingredients, this work showed the importance of testing them through international bodies' recommendations to accelerate the bench-to-market transition. Lastly, the macroalgae supply chain can be a viable and key source of renewable ingredients to promote a sustainable economy and attend to most of the 17 SDGs of the United Nations.

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#### References

- 1. Directorate-General for Research and Innovation (European Commission). A Sustainable Bioeconomy for Europe: Strengthening the Connection between Economy, Society and the Environment: Updated Bioeconomy Strategy; Publications Office Belgium: Brussels, Belgium, 2018.
- 2. Executive Agency for Small and Medium-sized Enterprises. *Blue Bioeconomy Forum: Highlights: Synthesis of the Roadmap and a Selection of Viable and Innovative Projects;* Publications Office Luxembourg: Luxembourg, 2020.
- ISO 16128-2:2017; Cosmetics—Guidelines on Technical Definitions and Criteria for Natural and Organic Cosmetic Ingredients—Part 2: Criteria for Ingredients and Products. ISO: Geneva, Switzerland, 2017. Available online: https: //www.iso.org/standard/65197.html (accessed on 11 July 2022).
- 4. United Nations. Transforming Our World: The 2030 Agenda for Sustainable Development (A/RES/70/1). 2015. Available online: https://sdgs.un.org/2030agenda (accessed on 15 July 2022).
- Cardozo, K.H.M.; Guaratini, T.; Barros, M.P.; Falcão, V.R.; Tonon, A.P.; Lopes, N.P.; Campos, S.; Torres, M.A.; Souza, A.O.; Colepicolo, P.; et al. Metabolites from algae with economical impact. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* 2007, 146, 60–78. [CrossRef] [PubMed]
- 6. Chambers, E. Sensory Testing Methods; Wolf, M.B., Ed.; ASTM: West Conshohocken, PA, USA, 1996.
- Milstein, S.R.; Halper, A.R.; Katz, L.M. Regulatory Requirements for the Marketing of Cosmetics in the United States. In Handbook of Cosmetic Science and Technology; CRC Press: Boca Raton, FL, USA, 2006; pp. 862–889.
- 8. Couteau, C.; Coiffard, L. Seaweed application in cosmetics. In *Seaweed in Health and Disease Prevention*; Academic Press: Cambridge, MA, USA, 2016; pp. 423–441.
- 9. Guiry, M.D.; Guiry, G.M. AlgaeBase. Available online: https://www.algaebase.org/ (accessed on 10 November 2022).

- Naga, S.; Neha, M.; Vitika, V. Seaweed Protein Market by Source (Red, Brown, Green), by Application (Food, Animal Feed and Additives, Cosmetics and Personal Care, Others): Global Opportunity Analysis and Industry Forecast, 2021–2030; Allied Market Research: Portland, OR, USA, 2022; p. 293. Available online: https://www.alliedmarketresearch.com/seaweed-protein-market-A16894 (accessed on 23 November 2022).
- 11. Stengel, D.B.; Connan, S.; Popper, Z.A. Algal chemodiversity and bioactivity: Sources of natural variability and implications for commercial application. *Biotechnol. Adv.* 2011, 29, 483–501. [CrossRef]
- Kok, J.M.L.; Jee, J.M.; Chew, L.Y.; Wong, C.L. The potential of the brown seaweed Sargassum polycystum against acne vulgaris. J. Appl. Phycol. 2016, 28, 3127–3133. [CrossRef]
- 13. Ozanne, H.; Toumi, H.; Roubinet, B.; Landemarre, L.; Lespessailles, E.; Daniellou, R.; Cesaro, A. Laminarin Effects, a β-(1,3)-Glucan, on Skin Cell Inflammation and Oxidation. *Cosmetics* **2020**, *7*, 66.
- Wang, L.; Oh, J.Y.; Jayawardena, T.U.; Jeon, Y.J.; Ryu, B. Anti-inflammatory and anti-melanogenesis activities of sulfated polysaccharides isolated from *Hizikia fusiforme*: Short communication. *Int. J. Biol. Macromol.* 2020, 142, 545–550. [CrossRef] [PubMed]
- 15. Januário, A.P.; Félix, R.; Félix, C.; Reboleira, J.; Valentão, P.; Lemos, M.F.L. Red Seaweed-Derived Compounds as a Potential New Approach for Acne Vulgaris Care. *Pharmaceutics* **2021**, *13*, 1930. [CrossRef]
- Kalasariya, H.S.; Yadav, V.K.; Yadav, K.K.; Tirth, V.; Algahtani, A.; Islam, S.; Gupta, N.; Jeon, B.-H. Seaweed-Based Molecules and Their Potential Biological Activities: An Eco-Sustainable Cosmetics. *Molecules* 2021, 26, 5313.
- 17. Berthon, J.Y.; Nachat-Kappes, R.; Bey, M.; Cadoret, J.P.; Renimel, I.; Filaire, E. Marine algae as attractive source to skin care. *Free Radic. Res.* 2017, *51*, 555–567. [CrossRef]
- Pangestuti, R.; Shin, K.H.; Kim, S.K. Anti-Photoaging and Potential Skin Health Benefits of Seaweeds. *Mar. Drugs* 2021, 19, 172. [CrossRef]
- Lee, M.K.; Ryu, H.; Lee, J.Y.; Jeong, H.H.; Baek, J.; Van, J.Y.; Kim, M.J.; Jung, W.K.; Lee, B. Potential Beneficial Effects of Sargassum spp. in Skin Aging. Mar. Drugs 2022, 20, 540. [CrossRef]
- 20. Meinita, M.D.N.; Harwanto, D.; Tirtawijaya, G.; Negara, B.; Sohn, J.H.; Kim, J.S.; Choi, J.S. Fucosterol of Marine Macroalgae: Bioactivity, Safety and Toxicity on Organism. *Mar. Drugs* **2021**, *19*, 545. [CrossRef]
- Fernando, I.P.S.; Dias, M.K.H.M.; Madusanka, D.M.D.; Han, E.J.; Kim, M.J.; Jeon, Y.J.; Ahn, G. Step gradient alcohol precipitation for the purification of low molecular weight fucoidan from *Sargassum siliquastrum* and its UVB protective effects. *Int. J. Biol. Macromol.* 2020, 163, 26–35. [CrossRef] [PubMed]
- 22. D'Orazio, N.; Gemello, E.; Gammone, M.A.; de Girolamo, M.; Ficoneri, C.; Riccioni, G. Fucoxantin: A Treasure from the Sea. *Mar. Drugs* **2012**, *10*, 604–616. [CrossRef]
- Freitas, R.; Martins, A.; Silva, J.; Alves, C.; Pinteus, S.; Alves, J.; Teodoro, F.; Ribeiro, H.M.; Goncalves, L.; Petrovski, Z.; et al. Highlighting the Biological Potential of the Brown Seaweed Fucus spiralis for Skin Applications. *Antioxidants* 2020, *9*, 611. [CrossRef] [PubMed]
- Hannan, M.A.; Sohag, A.A.; Dash, R.; Haque, M.N.; Mohibbullah, M.; Oktaviani, D.F.; Hossain, M.T.; Choi, H.J.; Moon, I.S. Phytosterols of marine algae: Insights into the potential health benefits and molecular pharmacology. *Phytomedicine* 2020, 69, 153201. [CrossRef]
- 25. Jesumani, V.; Du, H.; Pei, P.B.; Zheng, C.Q.; Cheong, K.L.; Huang, N. Unravelling property of polysaccharides from *Sargassum* sp. as an anti-wrinkle and skin whitening property. *Int. J. Biol. Macromol.* **2019**, *140*, 216–224. [CrossRef]
- 26. Gam, D.; Park, J.H.; Hong, J.W.; Jeon, S.J.; Kim, J.H.; Kim, J.W. Effects of Sargassum thunbergii Extract on Skin Whitening and Anti-Wrinkling through Inhibition of TRP-1 and MMPs. *Molecules* **2021**, *26*, 7381. [CrossRef]
- 27. Wang, L.; Oh, J.Y.; Hwang, J.; Ko, J.Y.; Jeon, Y.J.; Ryu, B. In Vitro and In Vivo Antioxidant Activities of Polysaccharides Isolated from Celluclast-Assisted Extract of an Edible Brown Seaweed, Sargassum fulvellum. *Antioxidants* **2019**, *8*, 493. [CrossRef]
- Zhen, A.X.; Hyun, Y.J.; Piao, M.J.; Fernando, P.; Kang, K.A.; Ahn, M.J.; Yi, J.M.; Kang, H.K.; Koh, Y.S.; Lee, N.H.; et al. Eckol Inhibits Particulate Matter 2.5-Induced Skin Keratinocyte Damage via MAPK Signaling Pathway. *Mar. Drugs* 2019, 17, 444. [CrossRef] [PubMed]
- 29. Jesumani, V.; Du, H.; Pei, P.B.; Aslam, M.; Huang, N. Comparative study on skin protection activity of polyphenol-rich extract and polysaccharide-rich extract from Sargassum vachellianum. *PLoS ONE* **2020**, *15*, e0227308. [CrossRef]
- 30. Bilal, M.; Iqbal, H.M.N. Marine Seaweed Polysaccharides-Based Engineered Cues for the Modern Biomedical Sector. *Mar. Drugs* **2020**, *18*, 7. [CrossRef]
- Lu, X.X.; Qin, L.; Guo, M.; Geng, J.J.; Dong, S.T.; Wang, K.; Xu, H.; Qu, C.F.; Miao, J.L.; Liu, M. A novel alginate from Sargassum seaweed promotes diabetic wound healing by regulating oxidative stress and angiogenesis. *Carbohydr. Polym.* 2022, 289, 119437. [CrossRef] [PubMed]
- Usov, A.I.; Zelinsky, N.D. Chemical structures of algal polysaccharides. In *Functional Ingredients from Algae for Foods and Nutraceuticals*; Woodhead Publishing Series in Food Science, Technology and Nutrition: Amsterdam, The Netherlands, 2013; pp. 23–86.
- 33. Torabi, P.; Hamdami, N.; Keramat, J. Microwave-assisted extraction of sodium alginate from brown macroalgae Nizimuddinia zanardini, optimization and physicochemical properties. *Sep. Sci. Technol.* **2022**, *57*, 872–885. [CrossRef]
- Harwood, J.L. Algae: Critical Sources of Very Long-Chain Polyunsaturated Fatty Acids. *Biomolecules* 2019, 9, 708. [CrossRef] [PubMed]

- Francavilla, M.; Franchi, M.; Monteleone, M.; Caroppo, C. The Red Seaweed Gracilaria gracilis as a Multi Products Source. *Mar. Drugs* 2013, 11, 3754–3776. [CrossRef] [PubMed]
- Otero, P.; Quintana, S.E.; Reglero, G.; Fornari, T.; Garcia-Risco, M.R. Pressurized Liquid Extraction (PLE) as an Innovative Green Technology for the Effective Enrichment of Galician Algae Extracts with High Quality Fatty Acids and Antimicrobial and Antioxidant Properties. *Mar. Drugs* 2018, *16*, 156. [CrossRef]
- Singh, D.K.; Pathak, J.; Pandey, A.; Singh, V.; Ahmed, H.; Rajneesh; Kumar, D.; Sinha, R.P. Ultraviolet-screening compound mycosporine-like amino acids in cyanobacteria: Biosynthesis, functions, and applications. In *Advances in Cyanobacterial Biology*; Academic Press: Cambridge, MA, USA, 2020; pp. 219–233.
- Lalegerie, F.; Lajili, S.; Bedoux, G.; Taupin, L.; Stiger-Pouvreau, V.; Connan, S. Photo-protective compounds in red macroalgae from Brittany: Considerable diversity in mycosporine-like amino acids (MAAs). *Mar. Environ. Res.* 2019, 147, 37–48. [CrossRef]
- Bedoux, G.; Pliego-Cortes, H.; Dufau, C.; Hardouin, K.; Boulho, R.; Freile-Pelegrin, Y.; Robledo, D.; Bourgougnon, N. Production and properties of mycosporine-like amino acids isolated from seaweeds. *Seaweeds Around World State Art Perspect.* 2020, 95, 213–245. [CrossRef]
- 40. Rastogi, R.P.; Richa; Sinha, R.P.; Singh, S.P.; Hader, D.P. Photoprotective compounds from marine organisms. *J. Ind. Microbiol. Biotechnol.* **2010**, *37*, 537–558. [CrossRef]
- Rangel, K.C.; Villela, L.Z.; Pereira, K.D.; Colepicolo, P.; Debonsi, H.M.; Gaspar, L.R. Assessment of the photoprotective potential and toxicity of Antarctic red macroalgae extracts from *Curdiea racovitzae* and *Iridaea cordata* for cosmetic use. *Algal Res. Biomass Biofuels Bioprod.* 2020, 50, 101984. [CrossRef]
- 42. Jimenez-Lopez, C.; Pereira, A.G.; Lourenco-Lopes, C.; Garcia-Oliveira, P.; Cassani, L.; Fraga-Corral, M.; Prieto, M.A.; Simal-Gandara, J. Main bioactive phenolic compounds in marine algae and their mechanisms of action supporting potential health benefits. *Food Chem.* **2021**, 341, 128262. [CrossRef]
- Ahn, G.N.; Kim, K.N.; Cha, S.H.; Song, C.B.; Lee, J.; Heo, M.S.; Yeo, I.K.; Lee, N.H.; Jee, Y.H.; Kim, J.S.; et al. Antioxidant activities of phlorotannins purified from *Ecklonia cava* on free radical scavenging using ESR and H<sub>2</sub>O<sub>2</sub>-mediated DNA damage. *Eur. Food Res. Technol.* 2007, 226, 71–79. [CrossRef]
- Polo, L.K.; Chow, F. Variation of antioxidant capacity and antiviral activity of the brown seaweed Sargassum filipendula (Fucales, Ochrophyta) under UV radiation treatments. Appl. Phycol. 2022, 3, 260–273.
- 45. Tsao, R. Chemistry and Biochemistry of Dietary Polyphenols. Nutrients 2010, 2, 1231–1246. [CrossRef]
- 46. Saul, R.C.; Saraí, C.H.; Karen, L.H.; Luis, A.C.C.; María, I.E.A.; Laura, E.G.; José de Jesús, O.P.; Marco, A.L.M. Flavonoids: Important Biocompounds in Food. In *Flavonoids—From Biosynthesis to Human Health*; INTECH: Eagle, Creek, 2017; pp. 353–369.
- Castejon, N.; Thorarinsdottir, K.A.; Einarsdottir, R.; Kristbergsson, K.; Marteinsdottir, G. Exploring the Potential of Icelandic Seaweeds Extracts Produced by Aqueous Pulsed Electric Fields-Assisted Extraction for Cosmetic Applications. *Mar. Drugs* 2021, 19, 662. [CrossRef] [PubMed]
- 48. Brenner, M.; Hearing, V.J. The protective role of melanin against UV damage in human skin. *Photochem. Photobiol.* **2008**, 84, 539–549. [CrossRef]
- 49. Lee, S.Y.; Baek, N.; Nam, T.G. Natural, semisynthetic and synthetic tyrosinase inhibitors. J. Enzym. Inhib. Med. Chem. 2016, 31, 1–13. [CrossRef]
- Costa, L.S.; Fidelis, G.P.; Telles, C.B.S.; Dantas-Santos, N.; Camara, R.B.G.; Cordeiro, S.L.; Costa, M.; Almeida-Lima, J.; Melo-Silveira, R.F.; Oliveira, R.M.; et al. Antioxidant and Antiproliferative Activities of Heterofucans from the Seaweed Sargassum filipendula. Mar. Drugs 2011, 9, 952–966. [CrossRef]
- 51. Caferri, R.; Guardini, Z.; Bassi, R.; Dall'Osto, L. Assessing photoprotective functions of carotenoids in photosynthetic systems of plants and green algae. *Methods Enzym.* **2022**, 674, 53–84. [CrossRef]
- 52. Jahan, A.; Ahmad, I.Z.; Fatima, N.; Ansari, V.A.; Akhtar, J. Algal bioactive compounds in the cosmeceutical industry: A review. *Phycologia* **2017**, *56*, 410–422. [CrossRef]
- 53. Benveniste, P. Biosynthesis and accumulation of sterols. Annu. Rev. Plant Biol. 2004, 55, 429–457. [CrossRef]
- 54. Brufau, G.; Canela, M.A.; Rafecas, M. Phytosterols: Physiologic and metabolic aspects related to cholesterol-lowering properties. *Nutr. Res.* **2008**, *28*, 217–225. [CrossRef]
- 55. RIBEIRO, C. Cosmetologia Aplicada a Dermoestética 2a Edição; Pharmabooks: Sao Paulo, Brazil, 2010.
- 56. Nohynek, G.J.; Antignac, E.; Re, T.; Toutain, H. Safety assessment of personal care products/cosmetics and their ingredients. *Toxicol. Appl. Pharmacol.* **2010**, 243, 239–259. [PubMed]
- 57. Suphasomboon, T.; Vassanadumrongdee, S. Toward sustainable consumption of green cosmetics and personal care products: The role of perceived value and ethical concern. *Sustain. Prod. Consum.* **2022**, *33*, 230–243. [CrossRef]
- Brooking, F. What Is the Clean Beauty Movement? Available online: https://pebblemag.com/magazine/living/clean-beautymovement (accessed on 22 June 2022).
- 59. Kolanjinathan, K.; Ganesh, P.; Saranraj, P. Pharmacological importance of seaweeds: A review. World J. Fish Mar. Sci. 2014, 6, 1–15.
- 60. Charlier, R.H.; Chaineux, M.-C.P. The healing sea: A sustainable coastal ocean resource: Thalassotherapy. *J. Coast. Res.* 2009, 25, 838–856. [CrossRef]
- 61. Fabrowska, J.; Kapuscinska, A.; Leska, B.; Feliksik-Skrobich, K.; Nowak, I. In vivo studies and stability study of Cladophora glomerata extract as a cosmetic active ingredient. *Acta Pol. Pharm.* **2017**, *74*, 633–641.

- 62. Samarakoon, K.; Jeon, Y.J. Bio-functionalities of proteins derived from marine algae—A review. *Food Res. Int.* **2012**, *48*, 948–960. [CrossRef]
- Hon, K.L.; Kung, J.S.C.; Ng, W.G.G.; Leung, T.F. Emollient treatment of atopic dermatitis: Latest evidence and clinical considerations. Drugs Context 2018, 7, 212530. [CrossRef]
- 64. Brummer, R.; Godersky, S. Rheological studies to objectify sensations occurring when cosmetic emulsions are applied to the skin. *J. Coast. Res.* **1999**, 152, 89–94. [CrossRef]
- 65. Ferreira, M.S.; Resende, D.; Lobo, J.M.S.; Sousa, E.; Almeida, I.F. Marine Ingredients for Sensitive Skin: Market Overview. *Mar. Drugs* **2021**, *19*, 464. [CrossRef]
- Groniger, A.; Sinha, R.P.; Klisch, M.; Hader, D.P. Photoprotective compounds in cyanobacteria, phytoplankton and macroalgae—A database. J. Photochem. Photobiol. B-Biol. 2000, 58, 115–122. [CrossRef]
- 67. Pangestuti, R.; Siahaan, E.A.; Kim, S.K. Photoprotective Substances Derived from Marine Algae. *Mar. Drugs* **2018**, *16*, 399. [CrossRef] [PubMed]
- Beaulieu, L.; Bondu, S.; Doiron, K.; Rioux, L.E.; Turgeon, S.L. Characterization of antibacterial activity from protein hydrolysates of the macroalga *Saccharina longicruris* and identification of peptides implied in bioactivity. *J. Funct. Foods* 2015, 17, 685–697. [CrossRef]
- Tyskiewicz, K.; Tyskiewicz, R.; Konkol, M.; Roj, E.; Jaroszuk-Scisel, J.; Skalicka-Wozniak, K. Antifungal Properties of *Fucus* vesiculosus L. Supercritical Fluid Extract Against *Fusarium culmorum* and *Fusarium oxysporum*. *Molecules* 2019, 24, 3518. [CrossRef] [PubMed]
- Soares, C.; Paiga, P.; Marques, M.; Neto, T.; Carvalho, A.P.; Paiva, A.; Simoes, P.; Costa, L.; Bernardo, A.; Fernandez, N.; et al. Multi-Step Subcritical Water Extracts of *Fucus vesiculosus* L. and *Codium tomentosum* Stackhouse: Composition, Health-Benefits and Safety. *Processes* 2021, 9, 893. [CrossRef]
- 71. Falkenberg, M.; Nakano, E.; Zambotti-Villela, L.; Zatelli, G.A.; Philippus, A.C.; Imamura, K.B.; Velasquez, A.M.A.; Freitas, R.P.; Tallarico, L.D.; Colepicolo, P.; et al. Bioactive compounds against neglected diseases isolated from macroalgae: A review. *J. Appl. Phycol.* 2019, *31*, 797–823. [CrossRef]
- 72. Prado, J.M.; Veggi, P.C.; Meireles, M.A.A. Extraction Methods for Obtaining Carotenoids from Vegetables—Review. *Curr. Anal. Chem.* **2014**, *10*, 29–66. [CrossRef]
- 73. Mustafa, A.; Turner, C. Pressurized liquid extraction as a green approach in food and herbal plants extraction: A review. *Anal. Chim. Acta* **2011**, *703*, 8–18. [CrossRef]
- Gbashi, S.; Adebo, O.A.; Piater, L.; Madala, N.E.; Njobeh, P.B. Subcritical Water Extraction of Biological Materials. Sep. Purif. Rev. 2017, 46, 21–34. [CrossRef]
- 75. Chan, C.H.; Yusoff, R.; Ngoh, G.C.; Kung, F.W.L. Microwave-assisted extractions of active ingredients from plants. *J. Chromatogr. A* **2011**, *1218*, 6213–6225. [CrossRef]
- Pinela, J.; Prieto, M.A.; Carvalho, A.M.; Barreiro, M.F.; Oliveira, M.B.P.P.; Barros, L.; Ferreira, I.C.F.R. Microwave-assisted extraction of phenolic acids and flavonoids and production of antioxidant ingredients from tomato: A nutraceutical-oriented optimization study. *Sep. Purif. Technol.* 2016, 164, 114–124. [CrossRef]
- 77. Alara, O.R.; Abdurahman, N.H.; Ukaegbu, C.I. Extraction of phenolic compounds: A review. *Curr. Res. Food Sci.* 2021, *4*, 200–214. [CrossRef] [PubMed]
- 78. Ktari, L.; Mdallel, C.; Aoun, B.; Ajjabi, L.C.; Sadok, S. Fucoxanthin and Phenolic Contents of Six Dictyotales From the Tunisian Coasts With an Emphasis for a Green Extraction Using a Supercritical CO<sub>2</sub> Method. *Front. Mar. Sci.* **2021**, *8*, 647159. [CrossRef]
- 79. Quitain, A.T.; Kai, T.; Sasaki, M.; Goto, M. Supercritical Carbon Dioxide Extraction of Fucoxanthin from *Undaria pinnatifida*. J. *Agric. Food Chem.* **2013**, *61*, 5792–5797. [CrossRef] [PubMed]
- 80. Ospina, M.; Castro-Vargas, H.I.; Parada-Alfonso, F. Antioxidant capacity of Colombian seaweeds: 1,. Extracts obtained from *Gracilaria mammillaris* by means of supercritical fluid extraction. *J. Supercrit. Fluids* **2017**, *128*, 314–322. [CrossRef]
- 81. Rozo, G.; Rozo, C.; Puyana, M.; Ramos, F.A.; Almonacid, C.; Castro, H. Two compounds of the Colombian algae Hypnea musciformis prevent oxidative damage in human low density lipoproteins LDLs. *J. Funct. Foods* **2019**, *60*, 103399. [CrossRef]
- Saravana, P.S.; Getachewac, A.T.; Cho, Y.J.; Choi, J.H.; Park, Y.B.; Woo, H.C.; Chun, B.S. Influence of co-solvents on fucoxanthin and phlorotannin recovery from brown seaweed using supercritical CO<sub>2</sub>. J. Supercrit. Fluids 2017, 120, 295–303. [CrossRef]
- 83. Fitzpatrick, L.J.; Zuloaga, O.; Etxebarria, N.; Dean, J.R. Environmental Applications of Pressurised Fluid Extraction. *Rev. Anal. Chem.* 2000, *19*, 75–122. [CrossRef]
- 84. Silva, E.K.; Martelli-Tosi, M.; Vardanega, R.; Nogueira, G.C.; Zabot, G.L.; Meireles, M.A.A. Technological characterization of biomass obtained from the turmeric and annatto processing by using green technologies. *J. Clean. Prod.* **2018**, *189*, 231–239. [CrossRef]
- Alcazar-Alay, S.C.; Osorio-Tobon, J.F.; Forster-Carneiro, T.; Meireles, M.A.A. Obtaining bixin from semi-defatted annatto seeds by a mechanical method and solvent extraction: Process integration and economic evaluation. *Food Res. Int.* 2017, *99*, 393–402. [CrossRef] [PubMed]
- Fayad, S.; Nehme, R.; Tannoury, M.; Lesellier, E.; Pichon, C.; Morin, P. Macroalga Padina pavonica water extracts obtained by pressurized liquid extraction and microwave-assisted extraction inhibit hyaluronidase activity as shown by capillary electrophoresis. J. Chromatogr. A 2017, 1497, 19–27. [CrossRef]

- Shibata, T.; Fujimoto, K.; Nagayama, K.; Yamaguchi, K.; Nakamura, T. Inhibitory activity of brown algal phlorotannins against hyaluronidase. *Int. J. Food Sci. Technol.* 2002, 37, 703–709. [CrossRef]
- 88. Heffernan, N.; Smyth, T.J.; FitzGerald, R.J.; Soler-Vila, A.; Brunton, N. Antioxidant activity and phenolic content of pressurised liquid and solid-liquid extracts from four Irish origin macroalgae. *Int. J. Food Sci. Technol.* **2014**, *49*, 1765–1772. [CrossRef]
- 89. Otero, P.; Lopez-Martinez, M.I.; Garcia-Risco, M.R. Application of pressurized liquid extraction (PLE) to obtain bioactive fatty acids and phenols from Laminaria ochroleuca collected in Galicia (NW Spain). *J. Pharm. Biomed. Anal.* **2019**, *164*, 86–92. [CrossRef]
- 90. Haraldsson, G. Separation of saturated/unsaturated fatty acids. J. Am. Oil Chem. Soc. **1984**, 61, 219–222. [CrossRef]
- Dobrincic, A.; Pedisic, S.; Zoric, Z.; Jurin, M.; Roje, M.; Coz-Rakovac, R.; Dragovic-Uzelac, V. Microwave Assisted Extraction and Pressurized Liquid Extraction of Sulfated Polysaccharides from *Fucus virsoides* and *Cystoseira barbata*. *Foods* 2021, 10, 1481. [CrossRef] [PubMed]
- Diop, C.I.K.; Beltran, S.; Jaime, I.; Sanz, M.T. Adjustable Gel Texture of Recovered Crude Agar Induced by Pressurized Hot Water Treatment of *Gelidium sesquipedale* Industry Waste Stream: An RSM Analysis. *Foods* 2022, 11, 2081. [CrossRef]
- Alboofetileh, M.; Rezaei, M.; Tabarsa, M.; You, S.; Mariatti, F.; Cravotto, G. Subcritical water extraction as an efficient technique to isolate biologically-active fucoidans from *Nizamuddinia zanardinii*. *Int. J. Biol. Macromol.* 2019, 128, 244–253. [CrossRef]
- Cheng, Y.; Xue, F.; Yu, S.; Du, S.; Yang, Y. Subcritical Water Extraction of Natural Products. *Molecules* 2021, 26, 4004. [CrossRef] [PubMed]
- Pangestuti, R.; Getachew, A.T.; Siahaan, E.A.; Chun, B.S. Characterization of functional materials derived from tropical red seaweed Hypnea musciformis produced by subcritical water extraction systems. J. Appl. Phycol. 2019, 31, 2517–2528. [CrossRef]
- 96. Florez-Fernandez, N.; Lopez-Garcia, M.; Gonzalez-Munoz, M.J.; Vilarino, J.M.L.; Dominguez, H. Ultrasound-assisted extraction of fucoidan from *Sargassum muticum*. J. Appl. Phycol. **2017**, 29, 1553–1561. [CrossRef]
- 97. Zhang, X.; Thomsen, M. Techno-economic and environmental assessment of novel biorefinery designs for sequential extraction of high-value biomolecules from brown macroalgae *Laminaria digitata*, *Fucus vesiculosus*; *Saccharina latissima*. *Algal Res.* **2021**, 60, 102499. [CrossRef]
- Beoletto, V.G.; De Las Mercedes Oliva, M.; Marioli, J.M.; Carezzano, M.E.; Demo, M.S. Antimicrobial Natural Products against Bacterial Biofilms. In *Antibiotic Resistance*; Elsevier: Amsterdam, The Netherlands, 2016; Volume 14, pp. 291–307.
- 99. Yuan, Y.; Macquarrie, D. Microwave assisted extraction of sulfated polysaccharides (fucoidan) from Ascophyllum nodosum and its antioxidant activity. *Carbohydr. Polym.* **2015**, *129*, 101–107. [CrossRef]
- Vázquez-Delfín, E.; Robledo, D.; Freile-Pelegrín, Y. Microwave-assisted extraction of the Carrageenan from *Hypnea musciformis* (Cystocloniaceae, Rhodophyta). J. Appl. Phycol. 2014, 26, 901–907. [CrossRef]
- Saravana, P.S.; Cho, Y.N.; Woo, H.C.; Chun, B.S. Green and efficient extraction of polysaccharides from brown seaweed by adding deep eutectic solvent in subcritical water hydrolysis. J. Clean. Prod. 2018, 198, 1474–1484. [CrossRef]
- 102. Park, J.S.; Han, J.M.; Surendhiran, D.; Chun, B.S. Physicochemical and biofunctional properties of *Sargassum thunbergii* extracts obtained from subcritical water extraction and conventional solvent extraction. *J. Supercrit. Fluids* **2022**, 182. [CrossRef]
- 103. Jang, J.H.; So, B.R.; Yeo, H.J.; Kang, H.J.; Kim, M.J.; Lee, J.J.; Jung, S.K.; Jung, Y.H. Preparation of cellulose microfibril (CMF) from *Gelidium amansii* and feasibility of CMF as a cosmetic ingredient. *Carbohydr. Polym.* **2021**, 257, 117569. [CrossRef]
- 104. Toan, T.Q.; Phong, T.D.; Tien, D.D.; Linh, N.M.; Anh, N.T.M.; Minh, P.T.H.; Duy, L.X.; Nghi, D.H.; Thi, H.H.P.; Nhut, P.T.; et al. Optimization of Microwave-Assisted Extraction of Phlorotannin from *Sargassum swartzii* (Turn.) C. Ag. with Ethanol/Water. *Nat. Prod. Commun.* 2021, 16, 1934578x21996184. [CrossRef]
- 105. Grillo, G.; Tabasso, S.; Solarino, R.; Cravotto, G.; Toson, C.; Ghedini, E.; Menegazzo, F.; Signoretto, M. From Seaweeds to Cosmeceutics: A Multidisciplinar Approach. *Sustainability* **2021**, *13*, 13443. [CrossRef]
- 106. Monde, L. Les enfants du talc Morhange Les Victimes D'intoxication à L'hexachlorophène ont Souffert, Selon une Étude de l'OMS, de Retards Dans Leur Développement Intellectuel. Available online: https://www.lemonde.fr/archives/article/1991/0 2/27/les-enfants-du-talc-morhange-les-victimes-d-intoxication-a-l-hexachlorophene-ont-souffert-selon-une-etude-de-l-omsde-retards-dans-leur-developpement-intellectuel\_4159753\_1819218.html (accessed on 13 July 2022).
- Eschner, K. Three Horrifying Pre-FDA Cosmetics. Available online: https://www.smithsonianmag.com/smart-news/threehorrifying-pre-fda-cosmetics-180963775/ (accessed on 2 February 2022).
- 108. OECD. OECD Test Guidelines for Chemicals—OECD. Available online: https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects\_20745788#:~:text=The%20OECD%20Guidelines%20for%20 the,characterise%20potential%20hazards%20of%20chemicals. (accessed on 13 July 2022).
- 109. Resende, D.I.S.P.; Ferreira, M.; Magalhaes, C.; Lobo, J.M.S.; Sousa, E.; Almeida, I.F. Trends in the use of marine ingredients in anti-aging cosmetics. *Algal Res. Biomass Biofuels Bioprod.* **2021**, *55*, 102273. [CrossRef]
- Dejoye Tanzi, C.; Abert Vian, M.; Ginies, C.; Elmaataoui, M.; Chemat, F. Terpenes as green solvents for extraction of oil from microalgae. *Molecules* 2012, 17, 8196–8205. [CrossRef]
- 111. Tavares, R.S.N.; Maria-Engler, S.S.; Colepicolo, P.; Debonsi, H.M.; Schafer-Korting, M.; Marx, U.; Gaspar, L.R.; Zoschke, C. Skin Irritation Testing beyond Tissue Viability: Fucoxanthin Effects on Inflammation, Homeostasis, and Metabolism. *Pharmaceutics* 2020, 12, 136. [CrossRef] [PubMed]
- 112. Pfuhler, S.; Pirow, R.; Downs, T.R.; Haase, A.; Hewitt, N.; Luch, A.; Merkel, M.; Petrick, C.; Said, A.; Schäfer-Korting, M.; et al. Validation of the 3D reconstructed human skin Comet assay, an animal-free alternative for following-up positive results from standard in vitro genotoxicity assays. *Mutagenesis* 2021, 36, 19–35. [CrossRef] [PubMed]

- 113. Carneiro, M.A.D.; Resende, J.F.D.; Oliveira, S.R.; Fernandes, F.D.; Borburema, H.D.D.; Barbosa-Silva, M.S.; Ferreira, A.B.G.; Marinho-Soriano, E. Performance of the agarophyte Gracilariopsis tenuifrons in a multi-trophic aquaculture system with Litopenaeus vannamei using water recirculation. *J. Appl. Phycol.* **2021**, *33*, 481–490. [CrossRef]
- 114. Kumar, B.R.; Mathimani, T.; Sudhakar, M.P.; Rajendran, K.; Nizami, A.S.; Brindhadevi, K.; Pugazhendhi, A. A state of the art review on the cultivation of algae for energy and other valuable products: Application, challenges, and opportunities. *Renew. Sustain. Energy Rev.* 2021, 138, 110649. [CrossRef]
- 115. Seghetta, M.; Marchi, M.; Thomsena, M.; Bjerre, A.B.; Bastianoni, S. Modelling biogenic carbon flow in a macroalgal biorefinery system. *Algal Res. Biomass Biofuels Bioprod.* **2016**, *18*, 144–155. [CrossRef]
- 116. Saral, J.S.; Ajmal, R.S.; Ranganathan, P. Bioeconomy of hydrocarbon biorefinery processes. In *Hydrocarbon Biorefinery*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 355–385.

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