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Review

Development of Bioactive Peptides Derived from Red Algae for Dermal Care Applications: Recent Advances

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Abstract: Bioactive peptides produced from proteinaceous red algae biomass with varied structures have garnered much attention in biological applications and production. Unfortunately, there have been few studies on developing approaches to feasible bioactive peptide production and purification. Our goal with this article is to explore the latest trends in easily applicable approaches for extracting bioactive peptides for cutaneous applications. Bibliometric statistics show that the number of scientific publications is growing, with Asia ranking as the highest producer. Peptide purity and bioactivity are the most important factors to consider while extracting and identifying peptides using various separation techniques. To generate novel bioactive peptides with high yield and low cost, future research should focus on increasing the yields and improving the separation methods. Moreover, human clinical trials should be conducted to validate their potential health benefits. Thus, the final objective of this literature review was to give an insight into the bioactive properties of red algae-derived peptides, which have proven potential for dermal application with anti-melanogenic, collagenogenic, antioxidant, antiaging, and photoprotective activities, etc. Moreover, it covers the algal peptides' scope for use in nutraceuticals and pharmaceuticals, and future studies for their emerging applications.

Keywords: red algae; proteins; peptide; anti-melanogenic; photoprotective

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1. Introduction

The marine ecosystem consists of various biotic resources, including seaweeds, which are a novel source of functional compounds, particularly peptides from algal sources. Among all the seaweeds, red seaweeds are considered primitive in the phylogenetic tree [1], and have been consumed for years as food supplements for healthy living. Bioactive peptides or cryptides are present in their parent proteins in a chemically inert state. They are released during the process of extraction as biologically active peptides. Bioactive peptides typically contain between 3 and 40 amino acids. The sequence and composition of these amino acids determine their activity. Industrial seaweed production has gained much attention globally due to its turnover of millions of dollars. This has dramatically increased after the publication of studies developing new drugs and value-added metabolites [2]. Algae have remarkable features in terms of high biomass productivity and adaptability to stress compared to terrestrial flora. This makes them a potent and cost-effective way for

the development of drugs for health and dermal applications [3]. As a result of population growth, food security issues have become one of the major concerns for food and agricultural industry to meet nutritional demands with high nutritional values. Algae has gained widespread acceptance as a functional food and is emerging as a nutritional supplement to overcome the issue [4].

Red seaweeds are abundant in protein content (max. 10–47% of dry weight). Red seaweeds have comparable protein content to those of high-proteinaceous vegetables such as soybeans, where proteins make up 35% of the dry mass. Red seaweed peptide's bioactivity is due to special sequences of amino acids [5] and other functional groups. Thus, the development of drugs and functional food can be obtained from a natural origin rather than a chemical origin [6]. To obtain peptides with biofunctional activity, the target molecules must be efficiently purified and concentrated. Depending on the peptides of interest, several separation techniques have been used to enhance and concentrate particular fractions. Yet, some peptides with particular bioactivity can be promising for biological processes. Hence, they can be called multifunctional peptides.

Red algal peptides have therapeutic properties, and they can be classified into various classes: antioxidant, prebiotic, antidiabetic, anti-obesity, and immunomodulatory. *Eucheuma denticulatum*, a red alga, is known for its high astaxanthin, vitamin B, vitamin E, β-carotene, polyunsaturated fatty acid, and polyphenol content [7]. It reduces weight, blood pressure, treats diabetes, and facilitates the control of cholesterol metabolism [8]. Important amino acids such as tryptophan and lysine are frequently present in most algal species. Leucine and isoleucine are specifically present in red algae species at lower concentrations [9,10]. There has been an increase in lifestyle diseases and nutritional deficiency disorders due to declining nutritional food quality. To ease the concern, algae have gained widespread acceptance as a functional food and nutritional supplement [11]. This article reviews the different analytical procedures to extract and purify algal peptides from Rhodophytes, and assesses their application for dermal care. As bioactive peptides become increasingly important, proteins in red algae can be targeted with advanced technology to improve peptide yield. This will enable us to explore their health benefits [10]. In particular, this article deals with different extraction and purification procedures to investigate the sustainable production of peptides with anti-melanogenic and photoprotective activity for dermatologic applications. The current review topic meets the criteria of three sustainable development goals, including Goal 3: good health and well-being; Goal 8: decent work and economic growth; and Goal 9: industry, innovation, and infrastructure. The ocean covers Taiwan's entire coast, and most coastal regions are rich in diverse macroalgae species. Currently, our group is working on an algal biorefinery project using an integrated approach for multi-product sequential extraction, and this review is part of that integrated study. Red and brown algae are targeted in this project for sequential bioactive molecule extraction. The algal biomass used for protein or peptide extraction is subsequently used for polysaccharide extraction for bioactive oligosaccharide production. The residual biomass is ultimately used for biofuel production. Different algal groups possess structural diversity; hence, the various bioactive molecules extracted may have different degrees of bioactivity. The above scheme enhances algal biomass reusability for multiple products and fits well with sustainable development goals.

2. Marine Peptide Research Trend

In March 2023, studies were conducted to collect bibliometric data by searching for the term "Red algae, proteins, and peptides" on the topic of "red algae, extraction, and purification". In total, 291 overall publications were returned, of which 226 were peer-reviewed scientific publications from the years 2000–2023, as shown in Figure 1. The number of published documents per year over the period of 22 years was found to be 22 documents per year. Due to an increasing interest in marine peptides, the publication trend has increased and is expected to rise further in the coming years. These publications can provide insight into novel ideas in research related to marine peptides. The number of

publications and percentages from each country were calculated. We found 291 publications from 48 countries, of which Asian countries published the most with 119 publications, followed by North America, Europe, Australia, and other countries. Asia contributed 40.9% of total publications, followed by North America with 17.18%, Europe with 14.43%, and Australia (3.09%). This trend is expected to increase owing to the health benefits and applications of marine peptides.

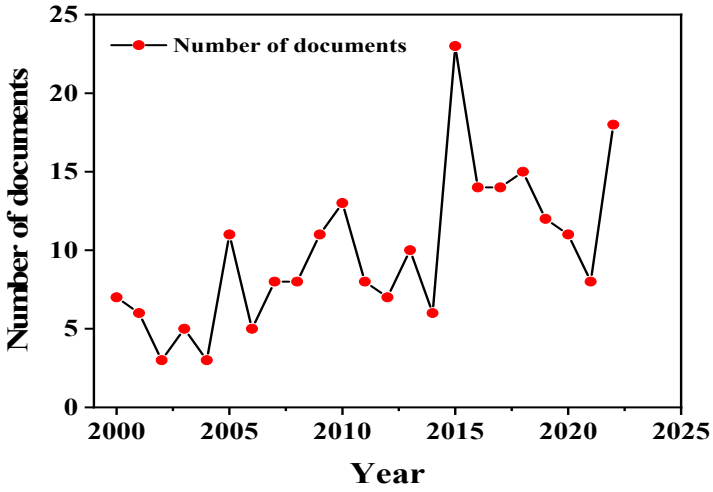

Figure 1. Trends in scientific publications in two decades.

To understand the co-occurrence of certain keywords in the field of production and purification of algal peptides, the search terms "Red algae" AND "Proteins" AND "Peptides" were searched in the Scopus database. These terms were searched for in the articles' title, keywords, and abstract (Figure 2). The data was analyzed over a period of 22 years, ranging from 2000 to 2023. Articles, reviews, and book chapters in English at the final publication stage were selected. A total of 291 keywords were retrieved and saved in Comma-Separated Values (CSV) format in Excel. In order to prevent replication of data and missing information, the data of all 291 entries was checked for duplicate entries.

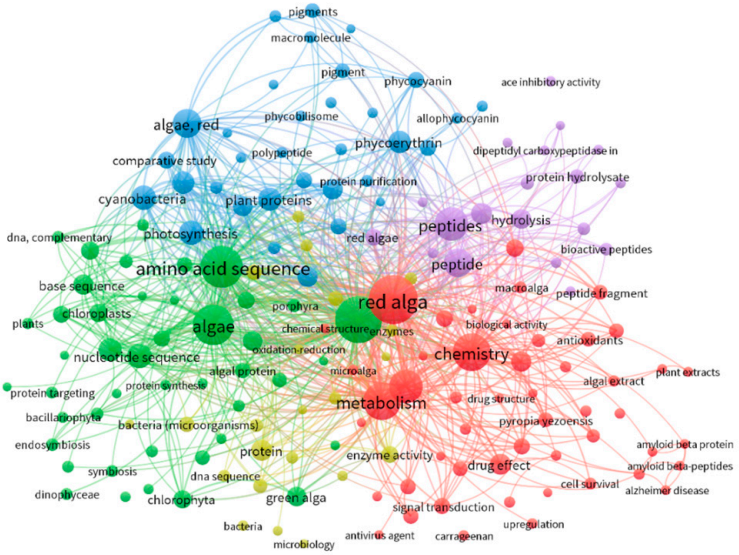

Figure 2. Co-occurrence network of keywords related to algal bioactive peptides.

Subsequently, the datasets were finalized and analyzed in VOS viewer for the co-occurrence of related index keywords. The keywords were evaluated for co-occurrence

analysis and counted. All 4498 of the identified keywords had a minimum threshold of seven occurrences, with 291 of them fulfilling the requirement. The remaining words were then evaluated, and the majority of similar keywords were manually screened and chosen based on how closely they connected to our interests and areas of research. Overall, 168 keywords were chosen and grouped into five clusters, with clusters 1, 2, 3, 4, and 5 containing 50, 44, 33, 22, and 19 items, respectively, in descending order. Based on this analysis, Figure 2 shows the co-occurrence network of specific keywords in the dataset. The larger dots in Figure 2 show current terms or trends which have been significantly used in previous work, smaller dots represent regions for future research on peptide extraction and purification.

These data represent the expanding research preferences and consciousness towards bioactive peptide extraction and purification from red seaweeds. Larger dots signify the importance of various peptide-derived amino acids sequences. Moreover, research trends show that the synthesis and health-promoting aspects of red algae are adequately covered, and red algae group is emerging as a platform showcasing promising health benefits among other seaweed groups reported for production of bioactive peptides. This article specifically deals with different extraction and purification procedures to ensure the extraction of peptides with antidiabetic, anti-melanogenic, and photoprotective activities.

3. Pretreatment of Algal Biomass for Peptide Extraction

Seaweeds, especially red seaweeds, are known to be rich in proteins, but the complex carbohydrate content of the cell wall prevents easy access to these proteins. Therefore, the cellular structure must be degraded during pretreatment to release the proteins. Several techniques are employed, including mechanical, physiochemical, and biological pretreatments. Moreover, pre-treatment removes impurities such as pigments, polysaccharides, phenolic compounds, lipids, etc., from the biomass prior to peptide synthesis [12,13].

Under physical methods, different mechanical forces are used to disrupt the cells, e.g., shear stress, ultrasonication, and microwave radiation [13]. A variety of mechanical pre-treatments are used to reduce the biomass size and crystallinity during cell integration, including ball milling, and high pressurized and high-speed homogenization [14,15]. Recent studies have reported that ultrasonication and microwave irradiation are better options for efficient pre-treatment [1,13,16]. Physical methods have major advantages such as easy operation, protection of cell function during degradation, time-efficient, low cost, and less contamination. However, long irradiation periods and high shear pressure destroy the cells. High energy consumption, high noise levels, and vibration also limit its function. Therefore, optimal conditions must be maintained during operation [13]. Apart from these methods, heat treatments such as steam explosion and autoclaving are used for pre-treatment. Chemical methods are another promising algal biomass pre-treatment method involving acids, alkaline solutions, and organic solvents as catalysts, such as CH_3ONa, CH_3OK, NaOH, KOH [13]. Chemical methods are often blended with physical methods for better results. Biological methods use various microbes and enzymes as pre-treatment agents. Biological methods have many advantages over physiochemical and mechanical methods, such as less time requirement, specificity, mild operating conditions, reduced energy consumption, low cost, low temperature requirement, and less aggression against cells than physiochemical and mechanical methods, which aid in releasing proteins and peptides with less cell structural damage. However, the composition, dosing, and operating conditions must be altered based on the biomass type and composition [12,13].

4. Synthesis/Extraction of Bioactive Peptides

Algae-derived bioactive peptides are synthesized by protein extraction. There is a significant polysaccharide fraction in the macroalgal cell wall, which is rigid in structure. For efficient extraction, cell rupturing, and removal of non-protein compounds are imperative. The techniques that have been used for algal protein extraction are summarized in Table 1, along with the standard operating conditions.

Table 1. Algal protein extraction and purification methods used for bioactive peptide production.

Algal Source	Pretreatment	Extraction Method	Protein Yield (% Dry Weight)	Purification Method	Reference
Porphyra umbilicalis	Alkali/acid	DI water stirring (Temp—8 °C, pH—12-2)	22.60	NA	[17]
Chondrus crispus	Sonication with salting down	Sonication (Temp—22 °C and $(NH_4)_2SO_4$ precipitation (80% *w*/*v*)	35.5	NA	[18]
Gracilaria sp.	Ultrasonic-assisted extraction/alkaline extraction	10% (*v*/*v*) NaOH and sonication (2 h)	86	Ion exchange chromatography	[19]
Chondracanthus chamissoi	Enzyme-assisted extraction	Enzyme/substrate ratio 1:10 at (pH 4.5, Temp—50 °C for 12 h)	36.10	NA	[20]
Palmaria palmata	Temperature/pressure-assisted extraction	Autoclaved (Temp—124 °C)	21.5	NA	[18]
Eucheuma cottonii	Ultrasonic-assisted extraction	Stirred (Temp—26 °C) and ultrasonicated	10.77 ± 0.42	RP-HPLC	[21]
Galdieria sulphuraria	Bead milling for effective cell disruption	Freezing thawing in liquid nitrogen	66.8	NA	[22]
Plocamium cartilagineum	Homogenization and filtration	Homogenization in water	23.18	NA	[14]
Palmaria palmata and *Porphyra umbilicalis*	Ball milling/homogenization and protein precipitation	6% TCA in water (*w*/*v*), (Temp—4 °C)	3.19–22.41	LC-MS/MS	[15]
Jania rubens	Hot water extraction and precipitation	Water (Temp—40 °C), precipitation using $ZnSO_4$ and $Ba(OH)_2$	11.3	NA	[23]

4.1. Solvent Extraction

The extraction technique for protein from seaweed is liable for polarity and peptide solubility. It uses liquid reagents such as DI water, buffers, acid/base solutions, lysis/surfactant-containing solutions, etc. [24]. Protein extraction for health applications should be carried out using non-toxic reagents. Purified water blending to permit algal cell autolysis prior to facilitating protein extraction is a form of green extraction. However, protein recovery is quite low for water-insoluble proteins compared to other liquid extraction techniques. It is notable that the sequential treatment of seaweeds with acid and alkaline solutions improves protein extraction efficiency [17]. However, in some cases, treatment with acid solutions only showed higher protein retrieval when using various solvents such as methanol, acetone, ethanol, hexane-ethyl acetate, and butanol [25]. Among other solvents, methanol was found to be effective in peptide separation with anti-microbial properties against 13 distinct pathogenic bacteria. A deep eutectic solvent (DES) was also found to be promising for peptide extraction in green technology and biological applications [26,27]. Based on the sample data, this approach is ineffective, and alternative technologies are required.

4.2. Chemical Hydrolysis

Chemical hydrolysis of proteins into peptides is achieved by breaking peptide bonds between different protein groups using an acidic or alkaline solution. It is carried out at high temperatures (121–138 °C) and pressures (220–310 mPa) for 2–8 h, followed by sample neutralization. A range of salts, especially calcium, sodium, or potassium hydroxides, are hydrolyzed at 27–54 °C under alkali conditions. Most reports on marine peptides focus on chemical hydrolysis utilizing sulfuric acid, nitric acid, acetic acid, phosphoric acid, maleic acid, and oxalic acid [28]. However, hydrochloric acid is the most common method for chemically hydrolyzing marine peptides. The use of acid followed by solubilization with alkaline solution releases polysaccharides and proteins from the cell wall matrix. This method improves protein recovery by facilitating protein solubilization via subsequent alkaline extraction [29]. *Porphyra umbilicalis* yielded a protein recovery of 22.60% (*w*/*w*), and this method was found to be more effective for red seaweeds [17]. O'connor et al. [18] described a method for peptide extraction with a protein recovery of 35.1% (1 h at 42 Hz) and was supported by salting out with 80% ammonium sulfate (*w*/*v*), followed by dialysis with a 3.5 kDa MWCO membrane. Acid hydrolysis is used more often than alkali hydrolysis. However, it has several disadvantages, which include higher sodium concentration, the and loss of essential amino acids such as tryptophan during the process. Despite this, HCL and NaOH are extensively employed in the industry for protein hydrolysis due to their ease of use and low cost. Thus, using chemical agents to hydrolyze proteins is inherently unfavorable due to its prolonged reaction time, fluctuating amino acid composition, usage of harsh chemicals, and alteration of chemical and functional characteristics [28].

4.3. Enzymatic Hydrolysis

The most popular technique for efficiently extracting bioactive peptides with the desired functionality is enzymatic hydrolysis. It is commonly used in the chemical, food, and pharmaceutical industries. Various polysaccharide-dissolving food-grade enzymes, e.g., cellulases, hemicellulases, glucanases, xylanases, and proteases, are used for macroalgae cell wall and polysaccharide disintegration [20,30]. It is a generally regarded as safe (GRAS) method of stabilizing peptides. To maximize protein/peptide extraction, it is important to determine the appropriate cell wall composition, specific enzyme, and their operating parameters (temperature, pH, and E:S ratio) based on species. The protein yield from red seaweed, *Chondracanthus chamissoi* was significantly higher when cellulase-assisted extraction was used, resulting in a 74.60% protein yield [20]. Protease-assisted extraction is more suitable than unmodified protein extraction for the direct synthesis of seaweed-derived BAPs since it releases proteins, peptides, and amino acids. In recent years, there has been a focus on improving peptide bioactivity by combining multiple proteases into multi-step hydrolysis and membrane-bioreactor technology, as well as pretreatment with enzymatic hydrolysis [31]. Low energy and by-product generation are major advantages of the enzymatic extraction of marine peptides. However, bottlenecks associated with enzymatic extraction, such as poor reaction rates and high monomer synthesis, must be solved. Combining enzymatic hydrolysis with additional techniques may result in high peptide yields with increased biological activities. Table 2 summarizes algal peptide production and bioactivity.

Table 2. Extraction and purification of bioactive peptides obtained from various red algae species and their bioactivities and potential application.

Source	Extraction Method	Purification Method	Bioactivity	Reference
Mazzaella japonica	Proteolysis without water extraction	RP-HPLC and MALDI-TOF/MS/MS	Cardio protective	[32]
Eucheuma cottonii	Ultra sonication and precipitation	RP-HPLC	Antioxidant peptides	[21]
Gracilariopsis chorda	Thermolysin hydrolysis	RP-HPLC	ACE inhibitory activity	[33]
Bangia fusco-purpurea	Enzymatic hydrolysis	Gel permeation and RP-HPLC	ACE inhibitory activity	[34]
Pyropia yezoensis	Industrial production (peptron korea)	(HPLC)	Antitumor, anti-fatigue, and anti-inflammatory activities, protect against UVA-induced photo-aging	[35]
Pyropia pseudolinearis	Cold water extraction	HPLC and MS	ACE inhibitory activity	[36]
(*Palmaria* sp.) *Dulse*	Enzymatic hydrolysis	RP-HPLC	ACE inhibitory activity, antihypertension	[37]
Gracilariopsis lemaneiformis	Enzymatic hydrolysis	Gel chromatography and AKTA pure system	Dietary supplement	[38]
Solieria filiformis	Alkaline precipitation	HPLC and MS	Antinociceptive and anti-inflammatory, effects, anti-cancerous activity	[39]
Grateloupia asiatica	Enzymatic hydrolysis	RP-HPLC	ACE inhibitory activity	[40]

4.4. Microbial Fermentation

Peptide synthesis using microbial fermentation is another a promising approach with high yield and GRAS status. The process involves a complex interplay between microbial strains, protein sources, and fermentation conditions. These can impact the yield and quality of the resulting peptides [41]. Further research is needed to optimize these factors and develop efficient and scalable methods for producing marine peptides with specific functional properties. Combining bacteria and yeast in a fermentation broth can result in the production of bioactive peptides that differ from those produced in a single microbe culture system. The co-culture of marine *Streptomyces* sp. and marine *Bacillus* sp. led to the identification of two novel piperazic acid-containing cyclic peptides [42]. Additionally, fermentation conditions can significantly influence marine peptides production. Fermentation duration may impact peptide antioxidant activities. As a result, variation in protein hydrolysates functioning can be influenced by changes in fermentation systems and peptide manufacturing procedures. Various contemporary fermentation methodologies are used to produce multifunctional peptides [42,43]. Recently lactic acid bacteria application

in raw material fermentation has been studied and reported [44]. Fermentation strategies are key approaches for advancement in isolating potential variants capable of creating novel bioactive peptides. This process has several advantages, including lower energy consumption, ecological sustainability, and economic reliability. The fundamental drawback of this approach is the sensitivity of the microbial fermentation system to contamination.

5. Purification of Peptides

Bioactive peptides are categorized by origin. Most of them are endogenous, rather than exogenous (acquired from diet) [45]. Several peptides have been discovered from complex macroalgal protein hydrolysates, which makes it difficult to identify their amino acid sequences. Aqueous, acidic, and alkaline extraction processes are employed for extracting peptides from their hydrolysates, which are separated and characterized utilizing several technologies [28]. Some of the most employed technologies are as follows.

5.1. Membrane Separation

Membrane separation is the most commonly used method for the separation of bioactive peptides from food sources using various micro-, membrane nano-, and ultra-filtration techniques. In membrane filtration, the sample is forced under pressure across a membrane with a predetermined molecular weight cut-off (MWCO), which retains the sample's non-hydrolyzed proteins while only allowing peptides to pass through. These fractionation methods are affordable and up-front. Membrane filtration systems face challenges related to their interaction with hydrophobic peptides, filtration of large molecules, membrane fouling and clogging, purity of peptides, and significant sample volumes [46]. Therefore, in addition to membrane filtration, other methods can be combined to address these limitations.

5.2. Chromatography

Chromatography is a crucial physiochemical technique used for peptide purification. Some of the most widely used methods include ion exchange, size exclusion, liquid-solid adsorption, and liquid–liquid partition chromatography coupled with UV diode array, fluorescence, and mass detectors. Specifically, peptides analyzed in the UV region between 210–220 nm are detected by silica-based columns (pH 2–8). Similarly, peptide separation with HPLC utilizes reverse-phase columns comprising hydrophobic packings, where the binding intensity of peptide changes with respect to net surface hydrophobicity. Acetonitrile (stronger) and methanol (weaker) are the two commonly used eluting solvents. Comparative analysis of peptides based on hydrophobicity is possible with this kind of peptide separation [47]. Even though these methods are time-consuming and expensive, because of their selectivity and resolution, they can be used to isolate and purify a wide range of complex elements, including marine algal peptides [48].

5.3. Capillary Electrophoresis

Capillary electrophoresis is an investigative method for analyzing peptides based on charge-to-mass ratios, affinity, sizes, hydrophobicity/hydrophilicity. There are a variety of preferred methods of protein separation with different background electrolyte migration mobilities. These methods include isoelectric focusing, isotachophoresis, and displacement electrophoresis. The ionic strength and pH of the background electrolyte affect protein migration, which determines the speed and resolution of proteins [49]. A simplistic conjoined glass capillary tube 100 cm $\times$ 100 μm is used. The method offers lower organic solvent utilization, high time efficiency, lower operating costs, high selectivity, and higher resolution [50]. In conclusion, capillary electrophoresis technology is widely used for peptide isolation due to its high efficiency, resolution, and selectivity. Nevertheless, the disadvantages of this method include limited susceptibility and low sensing limits.

6. Potential Cutaneous Bioactivities and Applications

6.1. Dermal Protective Properties

Skin acts as a primary barrier against the detrimental effects of the environment and prevents dehydration. Aging occurs internally and externally due to extreme exposure to the outside environment. External skin aging primarily arises from continuous vulnerability to heat, smoking, pollution, radiations (photoaging), stress, and an unhealthy lifestyle, whereas internal or chronological skin aging includes irreversible natural aging while growing or owing to hereditary causes [51]. Coarse wrinkles, dry skin, decreased elasticity, suppleness, and the appearance of a rough texture are typically caused by the cumulative effects of exposure to external elements on skin. Seaweeds are gaining increasing attention due to their diverse bioactive substances vital for skin health. These substances are minerals, proteins, vitamins, and carbohydrates [52], which are comparable to human plasma, and their nutrients are readily absorbed by the skin. Some algal extracts are used in skin care products, e.g., moisturizers, facial cleansing, masks, makeup removers, and bathing products because of their high mineral content [53] which refers to skin suppleness while reducing the effect of irritation, blemishes, and UV damage.

These extracts elicit a response by UV absorbers to harmful radiations (A and B) via bioactive phenolic compounds, mycosporine, amino acids, and carotenoids [54]. Red seaweed extracts from *Asparagopsis armata, Gelidium corneum,* and *Corallina officinalis* exhibit skin softening, complexion brightening, enhancing elasticity and anti-aging qualities, making them suitable for use in skincare products such as creams, oils, soap, masks, and lotions [2]. Agarose is derived from *Gracilaria* sp. It has anti-melanogenic action by lowering the production of melanin, making it useful for skin-whitening treatments [55]. Palmitic acid and its derivative ascorbyl palmitate, an algal fatty acid, are exploited as emulsifying and antioxidant agents in cosmetics for anti-wrinkle and anti-aging properties [56]. Mycosporine from several Rhodophytes has antioxidant effects and serves as a photoprotective ingredient in skin care products.

By 2025, the cosmetics market is projected to reach USD 69 billion, making it extremely competitive. Organic, herbal, and ayurvedic substances are used in cosmetic formulations by several manufacturers globally due to growing interest in wellbeing. The skin-whitening product market has expanded significantly as consumer demands increase. It was worth roughly USD 4075 million in 2017 and is projected to be worth approx. USD 8895 million by 2024, according to Zion Market Research (2019). Depigmentation markets exist in Europe, North America, Asia–Pacific, Latin America, the Middle East, and Africa. In 2017, due to rising demand in China, India, Japan, and Korea, the Asia–Pacific region accounted for the greatest market share for whitening skin care products [57].

6.2. Photo Protective Activity

UVA (315–400 nm) and UVB (280–315 nm) radiation is emitted by the sun, with UVA accounting for 95% of total radiation and UVB accounting for the remaining 5%. UVA and UVB both cause DNA damage, tissue swelling, and eventually cancer [58]. UV radiation increases the accumulation of ROS, resulting in oxidative stress which is closely related to the development of cancer and photoaging [59]. Although the skin has evolved to provide a defense mechanism, it should not be overlooked that these strategies are initially triggered in response to cell damage. Therefore, the photoprotective mechanism does not cure the damage caused to the cells, but instead stops additional damage. As a result, researchers and dermatologists have suggested using topical photoprotective compounds to prevent UVR-induced skin cell damage and hyperpigmentation at the same time. The production of photosynthetic compounds by red algae in response to the detrimental effects of UV radiation, such as reduced growth and reproduction, helps them survive in the harsh-UVR environment. Due to the production of many secondary metabolites such as phlorotannin, carotenoids (xanthophyll), and MAAs (mycosporine-like amino acids), red algae show photoprotective activity [60]. MAAs are considered nature's best UVA stabilizers, and some may also have antioxidant properties [61]. There are more MAAs in red seaweed species

than brown and green ones. Researchers have focused on analyzing the effectiveness of red algae as a photo-shielding compound, and various studies have determined DNA damage to cultured cells upon exposure. Most of the red algal species exhibited effective photo-protection against UVB radiation.

The commercially available algae extract used as a cosmetic ingredient in Helioguard 365®, derived from *Porphyra umbilicalis*, is used for skin care. It primarily contains porphyra-334 and shinorine (2:1). To the best of our knowledge, no data on phototoxicity or eye problems caused by red algae extracts exist. These extracts are considered while developing skin care products, even though photoprotective compounds identified in marine extracts, such as MAAs, are used in cosmetic formulations. Recent research has shown that *C. racovitzae* extract decreased ROS generation by 20–30% and showed higher efficacy than quercetin and Helioguard 365® at 3% in a photoprotection assay against UVA-induced ROS. At the tested concentrations, red algae extracts are regarded as non-cytotoxic, non-phototoxic, and non-irritating. *C. racovitzae* extract demonstrated photoprotective ability in combating ROS and increasing UVB absorption of UV filters, which may have applications in anti-aging and sunscreen products [62].

6.3. Anti-Melanogenic Activity

Studies have aimed to find melanogenesis inhibitors from natural sources possessing stable efficacy and safety to treat cutaneous hyperpigmentation. The cellular melanin formation process is catalyzed by tyrosinase (Cu-containing enzyme), which combines with cysteine to produce a cysteinyl-dopa called melanin, and catalase inhibition helps melanin synthesis regression. Depigmentation agents or tyrosinase inhibitors such as e.g., ascorbic acid, sulphates, flavonoids, kojic acid, arbutin, hydroquinone, and licorice extracts, as well as synthetic inhibitors, can inhibit tyrosinase activity via acting as a potential replacement substrate, inhibiting in a competitive or non-competitive manner, or chelating properties [5]. Various depigmenting compounds, such as hydroquinone, are used as benchmarks in skin-whitening treatments and pigmentation deficiency, e.g., melasma, age spots, and pigmentation post-inflammation. It acts as a poor substrate and natural competitor for tyrosinase in the absence and presence of dopaquinone, as well as a potent melanogenesis process inhibitor by forming 1,2,4-trihydroxybenzene. Although hydroquinone has demonstrated excellent results in hyperpigmentation treatment, its use has also been linked to undesirable side effects, including exogenous chronosis and contact dermatitis. Therefore, its use is not advised, and it is prohibited to be used in cosmetics and drugs [63]. Besides hydroquinone, kojic acid is also a popular skin-brightening agent. It works by eliminating the Cu atoms of the tyrosinase enzyme, hindering its normal function. However, it showed less stability in cosmetic formulations and UV radiation exposure. Due to noticeable side effects from depigmenting compounds such as hydroquinone and kojic acid, depigmenting agents from natural sources have been explored, such as red algae. This indicates more investigation into red algae's potential as a potent alternative to a chemical that lightens the skin by suppressing tyrosinase [63]. In an in vitro investigation utilizing *P. yezoensis* extracts, collagen-degrading enzymes matrix metalloproteinase (MMP)-2 and MMP-9 were inhibited, while procollagen synthesis enzymes tyrosinase-related protein (TRP)-1 and TRP-2 were increased. Because of the enhanced collagen formation and decreased pigmentation caused by regulated melanogenesis, it assisted in the reduction of skin pigmentation and anti-aging process [57].

6.4. Collagenogenic Activity

The skin comprises a keratinized stratified epidermis and a collagen-rich dermal connective tissue layer. Due to exposure to environmental stress, reactive oxygen species are produced. This leads to a reduction in collagen production and the activity of enzymes such as matrix metalloproteinases and tissue inhibitor of metalloproteinases. Additionally, UVR and pollution can activate keratinocyte and fibroblast cell surface receptors. This can result in the breakdown of existing collagen and inhibition of new collagen synthesis. According

to Berthon et al. [11], marine algae peptides and amino acids that resemble mycosporine, polysaccharides, sulphated polysaccharides, glucosyl glycerols, pigments, and polyphenols help protect the skin from damage and oxidative stress. Various studies have been conducted to examine the collagenogenic effect of marine peptides. The *P. yezoensis* peptide PYP1-5 was investigated for collagen synthesis in the human dermal fibroblast cell line Hs27. This confirmed the presence of type 1 collagen expression by using enzyme-linked immunosorbent assay (ELISA), Western blot analysis, and quantitative PCR. Additionally, alteration in the number of enzymes as well as an increase in the levels of TIMP-1 and TIMP-2 (tissue inhibitor of metalloproteinases) protein and mRNA which inhibit the action of metalloproteins [35]. Several biotech firms are creating cutting-edge platforms to produce recombinant collagen without animal sources. One of these firms, CollPlant, has created a plant-based platform that efficiently produces human collagen. Spirulina peptides have been employed in various skin formulations (0.1–10%) for maintaining skin health by improving gloss and moisture content [64]. In red algae, such as *Jania rubens* and *Meristotheca dakarensis*, compounds called glycosaminoglycans are present, which can help improve skin hydration and firmness. These algae are abundant in type-1 and type-3 collagen, which maintain skin structure and elasticity [65]. More research is needed to fully understand the mechanisms of action and potential side effects of algal extracts for dermal applications.

6.5. Antioxidant Activity

The process of melanin formation in the dermis produces H_2O_2 as a byproduct. This involves the hydroxylation of tyrosine to L-dihydroxyphenylalanine (L-DOPA), oxidation of L-DOPA to dopachrome, and spontaneous conversion of indoles to eumelanin. When H_2O_2 is generated, melanocytes are subject to oxidative stress, which can eventually result in cell death. The presence of natural antioxidants such as catalase and glutathione helps lower H_2O_2 and keep the melanogenesis pathway redox reaction in balance. In response to UVR exposure, endogenous antioxidant levels may decline, and ROS accumulate in the cells. This event leads to the activation of melanogenesis pathway [63]. Antioxidants reduce the harmful amount of H_2O_2 in the cells, decreasing peroxidase activity and significantly reducing melanogenesis. One study showed that antioxidants could inhibit melanogenesis. Ascorbic acid, a well-known antioxidant, was used to support the study and it showed a reduction in melanogenic activity by scavenging o-quinone products and inhibiting their polymerization into eumelanin [66]. Red algae constitute bioactive substances such as carotenoids, polyphenols, fucoxanthin, and sulfated polysaccharides with significant antioxidant characteristics. Red algae antioxidant activity has been studied using DPPH, ABTS, Trolox equivalent antioxidant, ferric reducing antioxidant potential or FRAP assay, Phosphomolybdenum assay, and metal-chelating assay to find scavenging of reactive oxygen species. Various studies have indicated the antioxidant activity of red algae; however, the amount of efficacy varies within species [67]. Red algae such as *Hypnea muscformis*, *Rhodomela confervoides*, *Galaxaura rugosa*, and *Gracilaria verrucosa*, have demonstrated higher antioxidant activity comparable to that of known antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and ascorbic acid [68]. Therefore, they can be used as antioxidants and skin-whitening agents instead of BHA, BHT, and ascorbic acid, which have been linked to carcinogenicity. *Tolypiocladia glomerulata ceramiales*, *Bonnemaisoniales gigartinales*, *Rhodymeniales Gracilariales Halymeniales*, *Asparagopsis taxiformis* [69], *Kappaphycus alvarezii* [70], and Gromphadorhina oblongata [71] are examples of red algae that have demonstrated antioxidant potential using various extraction solvents such as methanol and ethanol. Among these solvents, the ethyl acetate extract demonstrated significantly higher antioxidant activity than other fractions. This conclusion was supported by findings from other studies [72]. It also showed that compounds extracted with medium polarity had the highest antioxidant activity. Additionally, ascorbic acid is known to be unstable when added to cosmetics. As a result, red algae could work well in place of other antioxidants.

6.6. Anti-Aging Activity

Ageing of skin is characterized by wrinkles, dark spots, loss of elasticity, dullness, and roughness of skin. Senescent cells express genes that initiate production of inflammatory cytokines, growth factors, and degradative enzymes. Exogenous causes including smoking, pollution, sunlight exposure, repeated motions of the muscles, and drugs can result in premature aging. Generation of ROS during cellular respiration and energy consumption makes cells inviable to control ROS effects leading to oxidative stress. This leads to a decrease in Keratinocytes, melanocytes, and fibroblast proliferation and migration, as well as cellular activity and protein production in the epidermis and dermis. Red algae are rich in sulphates, polysaccharides, carrageenan, mycosporine-like amino acids, and phenolic compounds that can act as free radical scavengers and antioxidants to prevent oxidative damage in humans [73]. Moisturizing agents, sunscreen components, antioxidants, vitamins, hydroxy acids, and skin-lightening agents are a few of the several types of natural antiaging substances [74]. The increasing interest in application of marine compounds over the past few decades has led to over 40 companies incorporating these substances into 293 anti-aging cosmetic formulations. The "topmost three" marine components are extracted from the red seaweeds *Kappaphycus alvarezii* and *Chondrus crispus*. Since 2011, *Chondrus crispus* has been utilized, and *Kappaphycus alvarezii* application has grown remarkably [75].

In the cosmetic industry, extracts from *Acanthophora spicifera* and *Kappaphycus alvarezii* have been employed in textile face masks for antiaging purposes [76]. Carrageenan helps moisturize skin by enhancing the suppleness and appearance of the skin thereby preventing antiaging. The extracts from *Palmaria palmata*, *Porphyra purpurea*, *Chondrus crispus*, *Mastocarpus stellatus*, *Gracilaria vermiculophylla*, and *Polysiphonia fucoides* contain the main phenolic acids useful as antiaging agents. These acids include gallic acids, protocatechuic acids, chlorogenic acids, and gentisic acids. Trolox equivalent antioxidant capacity (TEAC) and ferric reducing antioxidant power (FRAP) tests were used to assess the antioxidant properties of an extract of *Halymenia durvillaei*. The FRAP and TEAC tests yielded results of 182.29 $\pm$ 13.35 µM/mg dry extract and 1.67 $\pm$ 0.04 mM/mg dry extract, respectively [6]. Protocatechuic acid has also shown potential anti-aging effects by promoting type-1 collagen [77]. Chlorogenic acid's resilience against oxidative stress is well recognized. Chlorogenic acid has the potential to be used as an anti-aging agent by lowering ROS levels. Due to their antioxidant and antiaging characteristics, flavonoids are employed in antiaging therapies. Flavonoids improve skin hydration, skin elasticity, and collagen content [78]. Malonylshisonin and 4′-demalonylsalvianin, two of the anthocyanins that fall under flavonoids, are found in *Jania rubens* extract. Anthocyanins may provide UV radiation protection, slow down skin aging, and stop inflammation and lipid peroxidation [79]. Figure 3 illustrates the peptide extraction technologies for red algae and their dermal application, as reported in recent studies. Table 3 summarizes various bioactivities of red algae biomass-derived peptides from recent studies.

Table 3. Various bioactivities of red-algae-derived peptides from recent studies.

Source	Peptide Sequence	Activity	Reference
Gracilariopsis chorda	IDHY and LVVER	ACE inhibitory activity	[33]
Polysiphonia urceolata *Bangiafuscopurpurea*	ALLAGDPSVLEDR and VVGGTGPVDEWGIAGAR	ACE inhibitory activity	[34]
Mazzaella japonica	YRD, VSEGLD, TIMPHPR, GGPAT, SSNDYPI, SRIYNVKSNG, VDAHY, CPYDWV, YGDPDHY, NLGN and DFGVPGHEP	ACE inhibitory activity	[32]
Palmaria palmata	SDITRPGGNM	Antioxidant activity	[80]
Palmaria palmata	IRLIIVLMPILMA	Renin inhibitory activity	[32]
Porphyra yezoensis	NMEKGSSSVVSSRMKQ	Antithrombotic activity	[32]
Palmaria palmata	LRY	ACE inhibitory activity	[81]
Porphyra spp.	GGSK and ELS	α-Amylase inhibitory activity	[82]
Pyropia haitanensis	QTDDNHSNVLWAGFSR	Antiproliferative activity	[83]
Palmaria palmata	SDITRPGGNM	Antioxidant activity	[84]

Table 3. *Cont.*

Source	Peptide Sequence	Activity	Reference
Palmaria palmata	IRLIIVLMPILMA	Renin inhibitory activity, Anti-hypertensive activity in spontaneously hypertensive rats	[85]
Palmaria palmata	SDITRPGGNM	Antioxidant activity	[84]
Pyropia (Nori)	NMEKGSSSVVSSRM (+15.99) KQ	Anticoagulant activity	[86]

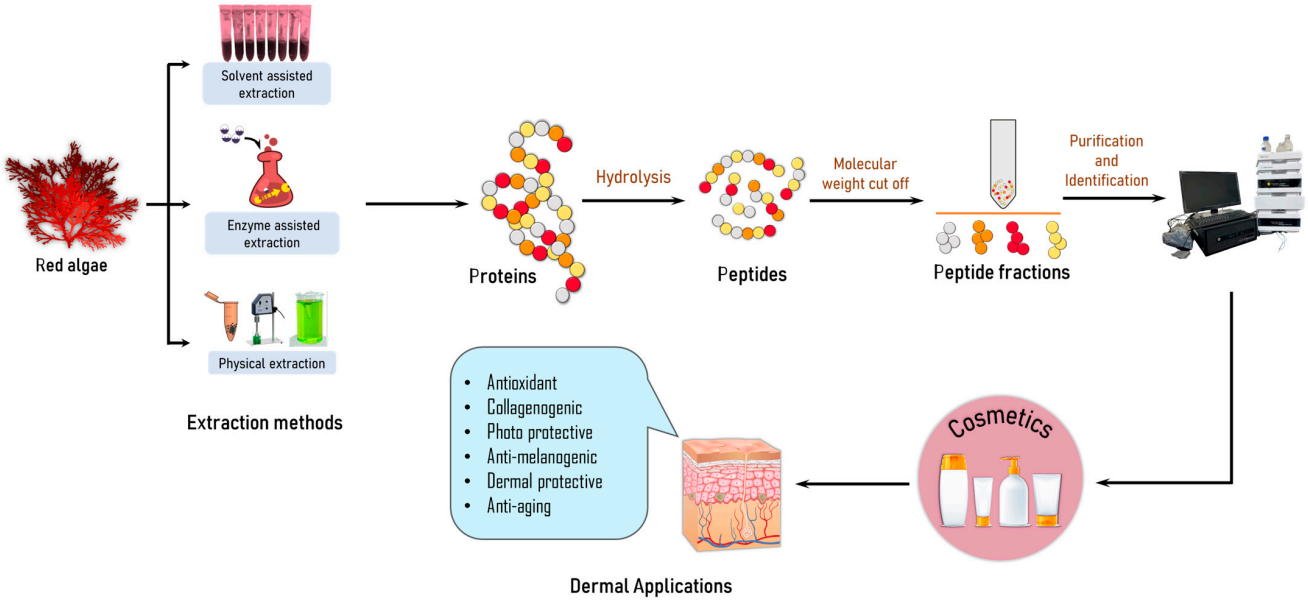

Figure 3. Schematic process of peptide extraction for dermal applications [34,39,54,57,74].

7. Future Perspectives and Challenges

As marine peptides have gained attention from the food, pharmaceutical, and cosmetic industries, it is necessary to exercise a thorough examination for toxicity and allergic reactions. Nevertheless, the toxicity of isolated chemicals from marine algae has not been identified in most research [87]. The authors of [88] analyzed the 86 novel peptides from *ulva lactula* for allergic and toxic effects, and 28 of them were found to be allergic. To ensure safe utilization and quality for commercialization, peptides and polysaccharides extracted from seaweeds must be examined for their physiological activity [1]. Some algal extracts and polysaccharides are already being used in commercial products for dermal application; however, well characterized peptides have yet to be developed for precise dermal application. For example, macroalgae extract reduced redness and blemishes, brightening, and sun damage, re-mineralizing, hydrating and firming the skin [89]. Their anti-UV properties are enhanced by the delivery of phenolic compounds, mycosporine, amino acids, and carotenoids, which provide UV absorption against UV-A and UV-B effects [54]. Red seaweed extracts from *Asparagopsis armata*, *Gelidium corneum*, and *Corallina officinalis* have skin-softening, whitening, and elasticity-restoring anti-aging properties when applied as creams, oils, soaps, masks, and lotions [2]. The anti-melanogenic activity of agarose from *Gracilaria cornea* and *G. lemaneiformis* makes it useful for skin whitening because it inhibits melanin synthesis [90,91]. Some anti-aging lotions are infused with amino acids derived from *Asparagopsis armata* [92]. Several Rhodophyta species contain mycosporine, which has antioxidant properties in skin care products [93].

Other health-promoting applications of algal peptides should also be considered, for expanding their scope. Recent findings suggest that naturally occurring polysaccharides from red seaweeds can serve as prebiotics by enhancing energy metabolism and affecting gut microbial balance. However, toxic oligosaccharides are produced by gut microbiota, which must be studied further for their potential to promote health through disease prevention [94]. Many edible products use bioactive peptides as functional components. The

two peptides Ile-Pro-Pro and Val-Pro-Pro have been utilized in the Japanese Calpis A meal-S drink, and Evolus, manufactured by Valio Ltd. They are derived from fermented milk protein and possess ACE-I-inhibiting characteristics and work as a vasodilator, reducing blood pressure in SHR models and human clinical trials. Further research is underway to extract similar peptides from algae. Moreover, studies aim to explore the influence of abiotic factors during food processing on the bioactivity of these peptides. However, for sustainable use, these peptides should be preserved at 23 °C.

8. Conclusions

Due to the growing demand for nutrition and health, algal peptides are gaining significant interest from the cosmeceutical industries. Algal peptides are a major source of skin care products due to their versatile and abundant existence. The presence of sulphated polysaccharides, mycosporine-like amino acids, carrageenan, flavonoids, and phenolic compounds in red algae makes them a viable component for sunscreens and cosmetics products from natural sources compared to chemically synthesized bioactive compounds. The cost-effective extraction and purification of bioactive peptides from red algae will be promising for the broader application of algal oligopeptides. Enzymatic hydrolysis, in combination with other extraction methods, provides peptides with relatively high yield, and bioactivity. Moreover, further research on seaweed sustainable growth and optimization for extraction and purification is needed to improve the commercial production of efficient bioactive compounds for dermal application. With promising cutaneous properties, bioactive peptides are being used in skin health promotion even though their mechanisms are yet to be defined fully. Additional peptide characterization, including proteomics, as well as human clinical trials are required to validate functional peptide cosmeceutical/nutraceutical claims. To maintain the algal peptide products for effective dermal application, adequate clinical trials are needed to determine skin irritation, absorption, allergens, genetic and phototoxicity, etc.

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References

1. Qiu, S.M.; Aweya, J.J.; Liu, X.; Liu, Y.; Tang, S.; Zhang, W.; Cheong, K.L. Bioactive polysaccharides from red seaweed as potent food supplements: A systematic review of their extraction, purification, and biological activities. *Carbohydr. Polym.* **2022**, *275*, 118696. [CrossRef]
2. Leandro, A.; Pereira, L.; Gonçalves, A.M.M. Diverse Applications of Marine Macroalgae. *Mar. Drugs* **2020**, *18*, 17. [CrossRef]
3. Pangestuti, R.; Kim, S.K. Seaweed proteins, peptides, and amino acids. In *Seaweed Sustainability*; Elsevier: Amsterdam, The Netherlands, 2015; pp. 125–140.
4. Ibañez, E.; Cifuentes, A. Benefits of using algae as natural sources of functional ingredients. *J. Sci. Food Agric.* **2013**, *93*, 703–709. [CrossRef]

5. Yuan, Y.; Jin, W.; Nazir, Y.; Fercher, C.; Blaskovich, M.A.; Cooper, M.A.; Barnard, R.T.; Ziora, Z.M. Tyrosinase inhibitors as potential antibacterial agents. *Eur. J. Med. Chem.* **2020**, *187*, 111892. [CrossRef]
6. Matanjun, P.; Mohamed, S.; Mustapha, N.M.; Muhammad, K.; Ming, C.H. Antioxidant activities and phenolics content of eight species of seaweeds from north Borneo. *J. Appl. Phycol.* **2008**, *20*, 367–373. [CrossRef]
7. Balasubramaniam, V.; June Chelyn, L.; Vimala, S.; Mohd Fairulnizal, M.N.; Brownlee, I.A.; Amin, I. Carotenoid composition and antioxidant potential of *Eucheuma denticulatum*, *Sargassum polycystum* and *Caulerpa lentillifera*. *Heliyon* **2020**, *6*, e04654. [CrossRef]
8. Balasubramaniam, V.; Aznyda, N.; Hussin, M.; Faradianna, L.; Aswir, A.R.; Mohd Fairulnizal, M.N. Effect of red edible seaweed *Eucheuma denticulatum* on diet-induced obesity In Vivo. *J. Appl. Phycol.* **2020**, *32*, 2407–2417. [CrossRef]
9. Astorga-España, M.S.; Rodríguez-Galdón, B.; Rodríguez-Rodríguez, E.M.; Díaz-Romero, C. Amino acid content in seaweeds from the Magellan Straits (Chile). *J. Food Compos. Anal.* **2016**, *53*, 77–84. [CrossRef]
10. Rawiwan, P.; Peng, Y.; Paramayuda, I.G.P.B.; Quek, S.Y. Red seaweed: A promising alternative protein source for global food sustainability. *Trends Food Sci. Technol.* **2022**, *123*, 37–56. [CrossRef]
11. 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]
12. O'connor, J.; Garcia-Vaquero, M.; Meaney, S.; Tiwari, B.K. Bioactive Peptides from Algae: Traditional and Novel Generation Strategies, Structure-Function Relationships, and Bioinformatics as Predictive Tools for Bioactivity. *Mar. Drugs* **2022**, *20*, 317. [CrossRef] [PubMed]
13. Krishnamoorthy, A.; Rodriguez, C.; Durrant, A. Sustainable Approaches to Microalgal Pre-Treatment Techniques for Biodiesel Production: A Review. *Sustainability* **2022**, *14*, 9953. [CrossRef]
14. Freitas, M.V.; Inácio, L.G.; Martins, M.; Afonso, C.; Pereira, L.; Mouga, T. Primary Composition and Pigments of 11 Red Seaweed Species from the Center of Portugal. *J. Mar. Sci. Eng.* **2022**, *10*, 1168. [CrossRef]
15. Niemi, C.; Mortensen, A.M.; Rautenberger, R.; Matsson, S.; Gorzsás, A.; Gentili, F.G. Rapid and accurate determination of protein content in North Atlantic seaweed by NIR and FTIR spectroscopies. *Food Chem.* **2023**, *404*, 134700. [CrossRef]
16. Pereira, A.G.; Jimenez-Lopez, C.; Fraga, M.; Lourenço-Lopes, C.; García-Oliveira, P.; Lorenzo, J.M.; Perez-Lamela, C.; Prieto, M.A.; Simal-Gandara, J. Extraction, Properties, and Applications of Bioactive Compounds Obtained from Microalgae. *Curr. Pharm. Des.* **2020**, *26*, 1929–1950. [CrossRef]
17. Harrysson, H.; Hayes, M.; Eimer, F.; Carlsson, N.; Toth, G.B.; Undeland, I. Production of protein extracts from Swedish red, green, and brown seaweeds, *Porphyra umbilicalis Kützing*, *Ulva lactuca Linnaeus*, and *Saccharina latissima* (Linnaeus) J. V. Lamouroux using three different methods. *J. Appl. Phycol.* **2018**, *30*, 3565–3580. [CrossRef]
18. O' Connor, J.; Meaney, S.; Williams, G.A.; Hayes, M. Extraction of Protein from Four Different Seaweeds Using Three Different Physical Pre-Treatment Strategies. *Molecules* **2020**, *25*, 2005. [CrossRef]
19. Kazir, M.; Abuhassira, Y.; Robin, A.; Nahor, O.; Luo, J.; Israel, A.; Golberg, A.; Livney, Y.D. Extraction of proteins from two marine macroalgae, *Ulva* sp. and *Gracilaria* sp., for food application, and evaluating digestibility, amino acid composition and antioxidant properties of the protein concentrates. *Food Hydrocoll.* **2019**, *87*, 194–203. [CrossRef]
20. Vásquez, V.; Martínez, R.; Bernal, C. Enzyme-assisted extraction of proteins from the seaweeds Macrocystis pyrifera and C hondracanthus chamissoi: Characterization of the extracts and their bioactive potential. *J. Appl. Phycol.* **2019**, *31*, 1999–2010. [CrossRef]
21. Sun, K.L.; Gao, M.; Wang, Y.Z.; Li, X.R.; Wang, P.; Wang, B. Antioxidant Peptides From Protein Hydrolysate of Marine Red Algae *Eucheuma cottonii*: Preparation, Identification, and Cytoprotective Mechanisms on H_2O_2 Oxidative Damaged HUVECs. *Front. Microbiol.* **2022**, *13*, 791248. [CrossRef]
22. Zhu, B.; Wei, D.; Pohnert, G. The thermoacidophilic red alga Galdieria sulphuraria is a highly efficient cell factory for ammonium recovery from ultrahigh-NH4+ industrial effluent with co-production of high-protein biomass by photo-fermentation. *Chem. Eng. J.* **2022**, *438*, 135598. [CrossRef]
23. Rifi, M.; Radwan, Z.; AlMonla, R.; Fajloun, Z.; Sabatier, J.M.; Kouzayha, A.; El-Sabban, M.; Mawlawi, H.; Dassouki, Z. The Lebanese Red Algae Jania rubens: Promising Biomolecules against Colon Cancer Cells. *Molecules* **2022**, *27*, 6617. [CrossRef] [PubMed]
24. Halim, R.; Harun, R.; Danquah, M.K.; Webley, P.A. Microalgal cell disruption for biofuel development. *Appl. Energy* **2012**, *91*, 116–121. [CrossRef]
25. Jeyasanta, I.; Sathish, N.; Patterson, J. Research article identification of bioactive peptides in Mussel species of Kanyakumari Coast. *Asian J. Biotechnol.* **2020**, *12*, 75–86. [CrossRef]
26. Singh, S.; Meena, P.; Saharan, V.K.; Bhoi, R.; George, S. Enhanced lipid recovery from *Chlorella* sp. Biomass by green approach: A combination of ultrasonication and homogenization pre-treatment techniques (hybrid method) using aqueous deep eutectic solvents. *Mater. Today Proc.* **2022**, *57*, 179–186. [CrossRef]
27. Sruthy, K.S.; Chaithanya, E.R.; Sathyan, N.; Anilkumar, P.R.; Singh, I.S.; Philip, R. Isolation, purification and characterization of antimicrobial peptides from Indian ruff, *Psenopsis cyanea* (Alcock, 1890). *Int. J. Res. Biol. Sci.* **2015**, *5*, 1–6.
28. Wang, X.; Yu, H.; Xing, R.; Li, P. Characterization, Preparation, and Purification of Marine Bioactive Peptides. *BioMed Res. Int.* **2017**, *2017*, 9746720. [CrossRef]
29. Ummat, V.; Sivagnanam, S.P.; Rajauria, G.; O'Donnell, C.; Tiwari, B.K. Advances in pre-treatment techniques and green extraction technologies for bioactives from seaweeds. *Trends Food Sci. Technol.* **2021**, *110*, 90–106. [CrossRef]

30. Harnedy, P.A.; FitzGerald, R.J. Extraction of protein from the macroalga *Palmaria palmata*. *LWT—Food Sci. Technol.* **2013**, *51*, 375–382. [CrossRef]
31. Akaberi, S.; Gusbeth, C.; Silve, A.; Senthilnathan, D.S.; Navarro-López, E.; Molina-Grima, E.; Müller, G.; Frey, W. Effect of pulsed electric field treatment on enzymatic hydrolysis of proteins of *Scenedesmus almeriensis*. *Algal Res.* **2019**, *43*, 101656. [CrossRef]
32. Kumagai, Y.; Kitade, Y.; Kobayashi, M.; Watanabe, K.; Kurita, H.; Takeda, H.; Yasui, H.; Kishimura, H. Identification of ACE inhibitory peptides from red alga *Mazzaella japonica*. *Eur. Food Res. Technol.* **2020**, *246*, 2225–2231. [CrossRef]
33. Mune Mune, M.A.; Miyabe, Y.; Shimizu, T.; Matsui, W.; Kumagai, Y.; Kishimura, H. Characterisation of Bioactive Peptides from Red Alga *Gracilariopsis chorda*. *Mar. Drugs* **2023**, *21*, 49. [CrossRef] [PubMed]
34. Wong, P.F.; Tan, L.J.; Nawi, H.; Abubakar, S. Proteomics of the red alga, *Gracilaria changii* (gracilariales, rhodophyta)1. *J. Phycol.* **2006**, *42*, 113–120. [CrossRef]
35. Kim, J.H.; Yun, E.J.; Yu, S.; Kim, K.H.; Kang, N.J. Different Levels of Skin Whitening Activity among 3,6-Anhydro-l-galactose, Agarooligosaccharides, and Neoagarooligosaccharides. *Mar. Drugs* **2017**, *15*, 321. [CrossRef]
36. Kumagai, Y.; Toji, K.; Katsukura, S.; Morikawa, R.; Uji, T.; Yasui, H.; Shimizu, T.; Kishimura, H. Characterization of ACE Inhibitory Peptides Prepared from *Pyropia pseudolinearis* Protein. *Mar. Drugs* **2021**, *19*, 200. [CrossRef]
37. Furuta, T.; Miyabe, Y.; Yasui, H.; Kinoshita, Y.; Kishimura, H. Angiotensin I Converting Enzyme Inhibitory Peptides Derived from Phycobiliproteins of Dulse *Palmaria palmata*. *Mar. Drugs* **2016**, *14*, 32. [CrossRef]
38. Cao, D.; Lv, X.; Xu, X.; Yu, H.; Sun, X.; Xu, N. Purification and identification of a novel ACE inhibitory peptide from marine alga *Gracilariopsis lemaneiformis* protein hydrolysate. *Eur. Food Res. Technol.* **2017**, *243*, 1829–1837. [CrossRef]
39. Chaves, R.P.; Silva, S.R.D.; Nascimento Neto, L.G.; Carneiro, R.F.; da Silva, A.L.C.; Sampaio, A.H.; de Sousa, B.L.; Cabral, M.G.; Videira, P.A.; Teixeira, E.H.; et al. Structural characterization of two isolectins from the marine red alga *Solieria filiformis* (Kützing) P.W. Gabrielson and their anticancer effect on MCF-7 breast cancer cells. *Int. J. Biol. Macromol.* **2018**, *107*, 1320–1329. [CrossRef]
40. Sumikawa, K.; Takei, K.; Kumagai, Y.; Shimizu, T.; Yasui, H.; Kishimura, H. In Silico Analysis of ACE Inhibitory Peptides from Chloroplast Proteins of Red Alga *Grateloupia asiatica*. *Mar. Biotechnol.* **2020**, *22*, 391–402. [CrossRef]
41. Abuine, R.; Rathnayake, A.U.; Byun, H.G. Biological activity of peptides purified from fish skin hydrolysates. *Fish. Aquat. Sci.* **2019**, *22*, 10. [CrossRef]
42. Shin, D.; Byun, W.S.; Moon, K.; Kwon, Y.; Bae, M.; Um, S.; Lee, S.K.; Oh, D.-C. Coculture of Marine *Streptomyces* sp. with *Bacillus* sp. Produces a New Piperazic Acid-Bearing Cyclic Peptide. *Front. Chem.* **2018**, *6*, 498. [CrossRef] [PubMed]
43. Lammi, C.; Aiello, G.; Boschin, G.; Arnoldi, A. Multifunctional peptides for the prevention of cardiovascular disease: A new concept in the area of bioactive food-derived peptides. *J. Funct. Foods* **2019**, *55*, 135–145. [CrossRef]
44. Mustafa, S.M.; Chua, L.S. Green technological fermentation for probioticated beverages for health enhancement. In *Biotechnological Progress and Beverage Consumption*; Grumezescu, A.M., Holban, A.M., Eds.; Academic Press: Cambridge, MA, USA, 2020; Volume 13, pp. 407–434.
45. Dary Guerra-Fajardo, L.; Pavón-Pérez, J.; Vallejos-Almirall, A.; Jorquera-Pereira, D. Advances in analytical techniques coupled to in vitro bioassays in the search for new peptides with functional activity in effect-directed analysis. *Food Chem.* **2022**, *397*, 133784. [CrossRef] [PubMed]
46. Acquah, C.; Chan, Y.W.; Pan, S.; Agyei, D.; Udenigwe, C.C. Structure-informed separation of bioactive peptides. *J. Food Biochem.* **2019**, *43*, e12765. [CrossRef]
47. Aluko, R.E. Food protein-derived peptides: Production, isolation, and purification. In *Proteins in Food Processing*, 2nd ed.; Yada, R.Y., Ed.; Woodhead Publishing: Sawston, UK, 2018; Volume 15, pp. 389–412.
48. Kim, S.S.; Ahn, C.B.; Moon, S.W.; Je, J.Y. Purification and antioxidant activities of peptides from sea squirt (Halocynthia roretzi) protein hydrolysates using pepsin hydrolysis. *Food Biosci.* **2018**, *25*, 128–133. [CrossRef]
49. Huang, Y.F.; Huang, C.C.; Hu, C.C.; Chang, H.T.J.E. Capillary electrophoresis-based separation techniques for the analysis of proteins. *Electrophoresis* **2006**, *27*, 3503–3522. [CrossRef]
50. Gomes, F.P.; Yates, J.R., III. Recent trends of capillary electrophoresis-mass spectrometry in proteomics research. *Mass Spectrom. Rev.* **2019**, *38*, 445–460. [CrossRef]
51. Zhang, S.; Duan, E.J.C. Fighting against Skin Aging: The Way from Bench to Bedside. *Cell Transplant.* **2018**, *27*, 729–738. [CrossRef]
52. Nova, P.; Martins, A.P.; Teixeira, C.; Abreu, H.; Silva, J.G.; Silva, A.M.; Freitas, A.C.; Gomes, A.M. Foods with microalgae and seaweeds fostering consumers health: A review on scientific and market innovations. *J. Appl. Phycol.* **2020**, *32*, 1789–1802. [CrossRef]
53. Quah, C.; Kim, K.; Lau, M.S.; Kim, W.; Cheah, S.; Gundamaraju, R. Pigmentation and dermal conservative effects of the astonishing algae *Sargassum polycystum* and *Padina tenuis* on guinea pigs, Human Epidermal Melanocytes (HEM) and Chang cells. *Afr. J. Tradit. Complement. Altern. Med.* **2014**, *11*, 77–83. [CrossRef]
54. Chan, J.N.; Poon, B.P.; Salvi, J.; Olsen, J.B.; Emili, A.; Mekhail, A. Perinuclear Cohibin Complexes Maintain Replicative Life Span via Roles at Distinct Silent Chromatin Domains. *Dev. Cell* **2011**, *20*, 867–879. [CrossRef] [PubMed]
55. Ismail, M.M.; Alotaibi, B.S.; El-Sheekh, M.M. Therapeutic Uses of Red Macroalgae. *Molecules* **2020**, *25*, 4411. [CrossRef] [PubMed]
56. Yarnpakdee, S.; Benjakul, S.; Senphan, T. Antioxidant activity of the extracts from freshwater macroalgae (*Cladophora glomerata*) grown in Northern Thailand and its preventive effect against lipid oxidation of refrigerated eastern little tuna slice. *Turk. J. Fish. Aquat.* **2018**, *19*, 209–219.

57. Park, J.; Lee, H.; Choi, S.; Pandey, L.K.; Depuydt, S.; De Saeger, J.; Park, J.T.; Han, T. Extracts of red seaweed, *Pyropia yezoensis*, inhibit melanogenesis but stimulate collagen synthesis. *J. Appl. Phycol.* **2021**, *33*, 653–662. [CrossRef]
58. Balupillai, A.; Nagarajan, R.P.; Ramasamy, K.; Govindasamy, K.; Muthusamy, G. Caffeic acid prevents UVB radiation induced photocarcinogenesis through regulation of PTEN signaling in human dermal fibroblasts and mouse skin. *Toxicol. Appl. Pharmacol.* **2018**, *352*, 87–96. [CrossRef]
59. Zhong, Q.Y.; Lin, B.; Chen, Y.T.; Huang, Y.P.; Feng, W.P.; Wu, Y.; Long, G.H.; Zou, Y.N.; Liu, Y.; Lin, B.-Q.; et al. Gender differences in UV-induced skin inflammation, skin carcinogenesis and systemic damage. *Environ. Toxicol. Pharmacol.* **2021**, *81*, 103512. [CrossRef] [PubMed]
60. Nowruzi, B.; Sarvari, G.; Blanco, S.J.A.R. The cosmetic application of cyanobacterial secondary metabolites. *Algal Res.* **2020**, *49*, 101959. [CrossRef]
61. Chrapusta, E.; Kaminski, A.; Duchnik, K.; Bober, B.; Adamski, M.; Bialczyk, J. Mycosporine-like amino acids: Potential health and beauty ingredients. *Mar. Drugs* **2017**, *15*, 326. [CrossRef]
62. Rangel, K.C.; Villela, L.Z.; Pereira, K.d.C.; 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.* **2020**, *50*, 101984. [CrossRef]
63. David, S.R.; Baharulnizam, N.B.; Rajabalaya, R. A review on biological assays of red algae marine compounds: An insight into skin whitening activities. *J. Herb. Med.* **2022**, *35*, 100585. [CrossRef]
64. Ariede, M.B.; Candido, T.M.; Jacome, A.L.M.; Robles Velasco, M.V.R.; João Carlos, M.; de Carvalho, A.R. Cosmetic attributes of algae—A review. *Algal Res.* **2017**, *25*, 483–487. [CrossRef]
65. Kalasariya, H.S.; Pereira, L.; Patel, N.B. Pioneering role of marine macroalgae in cosmeceuticals. *Phycology* **2022**, *2*, 172–203. [CrossRef]
66. Sánchez-Ferrer, A.; Rodríguez-López, J.N.; García-Cánovas, F.; García-Carmona, F. Tyrosinase: A comprehensive review of its mechanism. *Biochim. Biophys. Acta* **1995**, *1247*, 1–11. [CrossRef] [PubMed]
67. Sachindra, N.M.; Airanthi, M.K.W.A.; Hosokawa, M.; Miyashita, K. Radical scavenging and singlet oxygen quenching activity of extracts from Indian seaweeds. *J. Food Sci. Technol.* **2010**, *47*, 94–99. [CrossRef]
68. Hmani, I.; Ktari, L.; Ismail, A.; M'dallel, C.; El Bour, M. Assessment of the antioxidant and antibacterial properties of red algae (Rhodophyta) from the north coast of Tunisia. *Euro-Mediterr. J. Environ. Integr.* **2021**, *6*, 13. [CrossRef]
69. Neethu, P.V.; Suthindhiran, K.; Jayasri, M.A. Antioxidant and antiproliferative activity of *Asparagopsis taxiformis*. *Pharmacogn. Res.* **2017**, *9*, 238–246. [CrossRef]
70. Bhuyar, P.; Rahim, M.H.; Sundararaju, S.; Maniam, G.P.; Govindan, N. Antioxidant and antibacterial activity of red seaweed *Kappaphycus alvarezii* against pathogenic bacteria. *Glob. J. Environ. Sci. Manag.* **2020**, *6*, 47–58.
71. Nabil-Adam, A.; Shreadah, M.A. Red algae natural products for prevention of lipopolysaccharides (LPS)-induced liver and kidney inflammation and injuries. *Biosci. Rep.* **2021**, *41*, BSR20202022. [CrossRef]
72. Mellouk, Z.; Benammar, I.; Krouf, D.; Goudjil, M.; Okbi, M.; Malaisse, W. Antioxidant properties of the red alga *Asparagopsis taxiformis* collected on the North West Algerian coast. *Exp. Ther. Med.* **2017**, *13*, 3281–3290. [CrossRef]
73. Zhang, Q.; Li, N.; Liu, X.; Zhao, Z.; Li, Z.; Xu, Z. The structure of a sulfated galactan from *Porphyra haitanensis* and its In Vivo antioxidant activity. *Carbohydr. Res.* **2004**, *339*, 105–111. [CrossRef]
74. Ahmed, I.A.; Mikail, M.A.; Zamakshshari, N.; Abdullah, A.H. Natural anti-aging skincare: Role and potential. *Biogerontology* **2020**, *21*, 293–310. [CrossRef] [PubMed]
75. Resende, D.I.S.P.; Ferreira, M.; Magalhães, C.; Sousa Lobo, J.M.; Sousa, E.; Almeida, I.F. Trends in the use of marine ingredients in anti-aging cosmetics. *Algal Res.* **2021**, *55*, 102273. [CrossRef]
76. Janarthanan, M.; Senthil Kumar, M. Ontogenesis of textile face mask using cotton fabric by treating with red seaweeds extract for cosmetotextile applications. *J. Text. Inst.* **2019**, *110*, 959–971. [CrossRef]
77. Shin, S.; Cho, S.H.; Park, D.; Jung, E. Anti-skin aging properties of protocatechuic acid in vitro and In Vivo. *J. Cosmet. Dermatol.* **2020**, *19*, 977–984. [CrossRef] [PubMed]
78. Michalun, M.V.; DiNardo, J.C. *Skin Care and Cosmetic Ingredients Dictionary*; Cengage Learning: Boston, MA, USA, 2014.
79. Dixit, D.; Reddy, C.R.K. Non-targeted secondary metabolite profile study for deciphering the cosmeceutical potential of red marine macro alga *Jania rubens*-An LCMS-based approach. *Cosmetics* **2017**, *4*, 45. [CrossRef]
80. Lafarga, T.; Acién-Fernández, F.G.; Garcia-Vaquero, M. Bioactive peptides and carbohydrates from seaweed for food applications: Natural occurrence, isolation, purification, and identification. *Algal Res.* **2020**, *48*, 101909. [CrossRef]
81. Echave, J.; Fraga-Corral, M.; Garcia-Perez, P.; Popović-Djordjević, J.; Avdović, E.H.; Radulović, M.; Xiao, J.; Prieto, M.A.; Simal-Gandara, J. Seaweed protein hydrolysates and bioactive peptides: Extraction, purification, and applications. *Mar. Drugs* **2021**, *19*, 500. [CrossRef]
82. Admassu, H.; Gasmalla, M.A.; Yang, R.; Zhao, W. Identification of bioactive peptides with α-amylase inhibitory potential from enzymatic protein hydrolysates of red seaweed (*Porphyra* spp.). *J. Agric. Food Chem.* **2018**, *66*, 4872–4882. [CrossRef]
83. Mao, X.; Bai, L.; Fan, X.; Zhang, X. Anti-proliferation peptides from protein hydrolysates of *Pyropia haitanensis*. *J. Appl. Phycol.* **2017**, *29*, 1623–1633. [CrossRef]
84. Harnedy, P.A.; O'Keeffe, M.B.; FitzGerald, R.J. Fractionation and identification of antioxidant peptides from an enzymatically hydrolysed *Palmaria palmata* protein isolate. *Food Res. Int.* **2017**, *100*, 416–422. [CrossRef]

85. Fitzgerald, C.; Aluko, R.E.; Hossain, M.; Rai, D.K.; Hayes, M. Potential of a renin inhibitory peptide from the red seaweed *Palmaria palmata* as a functional food ingredient following confirmation and characterization of a hypotensive effect in spontaneously hypertensive rats. *J. Agric. Food Chem.* **2014**, *62*, 8352–8356. [CrossRef]
86. Indumathi, P.; Mehta, A. A novel anticoagulant peptide from the Nori hydrolysate. *J. Funct. Foods.* **2016**, *20*, 606–617. [CrossRef]
87. Berbudi, A.; Rahmadika, N.; Tjahjadi, A.I.; Ruslami, R. Type 2 diabetes and its impact on the immune system. *Curr. Diabetes Rev.* **2020**, *16*, 442–449. [CrossRef] [PubMed]
88. Garcia-Vaquero, M.; Mora, L.; Hayes, M. In Vitro and In Silico approaches to generating and identifying angiotensin-converting enzyme I inhibitory peptides from green macroalga Ulva Lactuca. *Mar. Drugs* **2019**, *17*, 204. [CrossRef] [PubMed]
89. Pereira, L. Seaweeds as source of bioactive substances and skin care therapy-cosmeceuticals, algotheraphy and thalassotherapy. *Cosmetics* **2018**, *5*, 68. [CrossRef]
90. Jin, M.; Liu, H.; Hou, Y.; Chan, Z.; Di, W.; Li, L.; Zeng, R. Preparation, characterization and alcoholic liver injury protective effects of algal oligosaccharides from *Gracilaria lemaneiformis*. *Food Res. Int.* **2017**, *100*, 186–195. [CrossRef]
91. Kim, C.R.; Kim, Y.M.; Lee, M.K.; Kim, I.H.; Choi, Y.H.; Nam, T.J. Pyropia yezoensis peptide promotes collagen synthesis by activating the TGF-β/Smad signaling pathway in the human dermal fibroblast cell line Hs27. *Int. J. Mol. Med.* **2017**, *39*, 31–38. [CrossRef] [PubMed]
92. Cotas, J.; Leandro, A.; Monteiro, P.; Pacheco, D.; Figueirinha, A.; Gonçalves, A.M.M.; da Silva, G.J.; Pereira, L. Seaweed phenolics, from extraction to applications. *Mar. Drugs* **2020**, *18*, 384. [CrossRef]
93. Torres, M.D.; Flórez-Fernández, N.; Domínguez, H. Integral utilization of red seaweed for bioactive production. *Mar. Drugs* **2019**, *17*, 314. [CrossRef]
94. Pan, L.; Cai, C.; Liu, C.; Liu, D.; Li, G.; Linhardt, R.J.; Yu, G. Recent progress and advanced technology in carbohydrate-based drug development. *Curr. Opin. Biotechnol.* **2021**, *69*, 191–198. [CrossRef]