Review

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Seaweed Superfoods: Bioactive Nutraceuticals for Coeliac Disease, Diabetes and Hyperglycemia Support

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Posted Date: 18 September 2023

doi: 10.20944/preprints202309.1159.v1

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Review

Seaweed Superfoods: Bioactive Nutraceuticals for Coeliac Disease, Diabetes and Hyperglycemia Support

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Abstract: The number of people with gluten-related illnesses has been increasing and the available treatments include the introduction of a gluten-free diet. In the bakery industry, there are problems with gluten-free products, namely the important characteristics that this component gives to doughs and the low nutritional value they present. A disease that has also increased in recent years is diabetes mellitus, which is characterized by a lack of insulin and the effectiveness of its action (type 1 diabetes) or tissue insensitivity to the hormone (type 2 diabetes). In terms of treatments, there are several approaches: inhibition of digestive enzymes (α-amylase and α-glucosidase) or techniques based on mechanisms of action (stimulation of insulin production and release, insulin transport and decreased glucose absorption). Hyperglycemia is also associated with the production of reactive oxygen species, which leads to cell apoptosis. On the other hand, there was also an association with high levels of cholesterol in the body, which contributed to the development of other types of diseases. In this sense, macroalgae have been studied as a source of natural compounds and used as food supplements, due to their protein, amino acid and mineral content, and the anti-diabetic effect in controlling the glycemic index, oxidative stress and cholesterol have already been demonstrated. Seaweed emerges as a promising source of bioactive nutraceuticals for individuals with coeliac disease, diabetes, and hyperglycemia. The rising prevalence of gluten-related illnesses calls for effective treatments, and seaweed's potential in enhancing the nutritional value of gluten-free products is noteworthy. Additionally, its demonstrated anti-diabetic effects, including glycemic index control, oxidative stress reduction, and cholesterol management, make it a valuable dietary supplement. Further research is needed to explore the specific bioactivities of seaweed compounds and their mechanisms of action. Integrating seaweed-based nutraceuticals into diets could complement traditional treatments, offering potential health benefits to those with coeliac disease and diabetes.

Keywords: seaweed; bioactive; nutraceuticals; coeliac disease; diabetes; hyperglycemia; glycemic index; cholesterol management

1. Introduction

Overweight/obesity, cardiovascular illnesses (such as arterial hypertension, myocardial infarction, and stroke), diabetes mellitus, digestive disease (such as, Coeliac disease), certain

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malignancies, and osteoporosis are all diet-related diseases. An improper diet also contributes considerably to the development of a group of illnesses known as metabolic syndrome. Diet-related diseases burden is predicted to rise in many nations as populations age and obesity rates rise. There are various dietary risk factors associated with illness development. However, high salt consumption, a lack of whole grains, and a lack of fruits are regarded as the most relevant dietary risk factors [1–5].

Although, the increasing incidence of new diseases and the rapid growth of diet-related diseases, there is a need to verify new or "old-new" raw source to promote a healthier food, not only raw food, but also, in processed food. With easy availability to highly processed foods, most sophisticated market economies' average diet quality is low. Thus, one of the hypotheses is to turn of how processed food is done and which ingredients are used. And how processed food can be modified to turn into more healthy solutions. Due to other solutions, like shifting the diet habits did appear to have enough success. Effective techniques are desperately required to change the health problems due to a bad nutrition and diet [6,7].

Macroalgae are one of the most promising sustainable foods raw sources. They have the ability for rapid development in the water, which simplifies the process of manufacturing while lowering production costs. Even though macroalgae have been used for millennia in Eastern nations such as China, Japan, and Korea as a raw food or processed food. Their introduction as a food source in Western society happened just a few decades ago, where the health is lowering, and diet-related diseases are increasing. To combat this dietary deficiency, seaweeds played an important role, as they are high in numerous macronutrients and micronutrients, such as vitamins, minerals, and proteins [8–12].

A high level of public knowledge of a balanced diet and nutrition is essential for reducing the burden of food-related illnesses. There is, however, a scarcity of scientific evidence on public knowledge of diet-related disorders and risk factors. Faced with the above-mentioned questions, this review aims to analyze how macroalgae can be game changer for diet-related diseases, though not-healthy food ingredients replacement by macroalgae or macroalgae components, which contain bioactive properties. Thus, observing the potential of macroalgae-based products in eminent diseases such as coeliac disease, or more common diseases, such as diabetes and cholesterol complications.

2. Diet-related diseases

2.1. Coeliac disease

Nowadays, the number of people with diseases related to the consumption of wheat and cereals containing gluten has been increasing. The most common diseases are coeliac disease, non-celiac gluten sensitivity (NCGS), wheat allergy or irritable bowel syndrome [13]. Coeliac disease is a specific immune response, triggered by gluten, that affects the small intestine, however, individuals are also genetically susceptible to developing it [14,15]. Gluten is a general term for alcohol-soluble proteins present in cereals such as wheat, rye, barley, and other derived products [16,17], and is mainly composed of gliadin and glutenin [15]. The high proline content in gluten makes it difficult to digest by human gastrointestinal enzymes [14].

Wheat allergy is caused by the consumption of insoluble gliadins, which are present in wheat and can react with immunoglobulin E (IgE). One of the differences between the two conditions is that coeliac disease causes permanent damage to the gastrointestinal system, and the only treatments available are to introduce a strict diet without the intake of gluten or wheat [16]. Foods such as conventional wheat bread are staple foods and are present in many people's diets due to their nutritional value and low price [18], so eliminating this food is not one of the goals [13].

In the bakery industry, attempts are made to produce gluten-free products that are equally flavorful and quality, however, some challenges need to be overcome, namely the characteristics that gluten imparts to bread doughs and the low protein content that these foods have [13]. In conventional bread production, starch binds water and creates a gas-permeable structure. Gluten traps carbon dioxide (CO_2), produced in the fermentation process by yeasts, which causes the dough

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to rise due to the presence of a minor component of gluten, the glutenin macropolymer (GMP), which imparts elastic properties to bread dough and allows it to rise [13]. Flours used as a substitute for wheat flour are rice and/or maize flours combined with starch, however, this type of mixture has a high amount of fat and salt and a low amount of protein, which affects the structure and quality of the bread [13]. Rice flour is widely used in gluten-free baking as it is a low-cost ingredient and its characteristics such as white color, mild taste and easy digestibility are suitable for bakery products [19]. However, despite the advantages described above, the functional qualities that this flour confers are not sufficient to obtain quality end products and therefore compounds such as hydrocolloids are added [19]. It is also possible to use pseudocereals which are used in the production of gluten-free products due to their nutritional value, high protein content, essential amino acids and fatty acids [20]. However, it is necessary to pay attention to the growing conditions of the plant species because it influences the composition of the cereals and the quality of the final product. Legume flours, such as chickpea, soya bean and cassava, are also an alternative to starch additives due to the water retention capacity they confer [20].

Proteins are basic substances for cells and are an essential nutrient, mainly obtained through the intake of animal or vegetable protein and soya products. Milk proteins are used because they have a high nutritional value and similar chemical structure to gluten proteins, however, they can be a limited and expensive resource [20,21]. The positive side of adding milk proteins is the availability of essential amino acids it contains. On the other hand, the addition of protein-rich and lactose-poor products, which is not always the case with milk, has been shown to increase the quality of the final product, and associations have been made with lactose intolerance in people with small bowel inflammation due to coeliac disease [20].

2.2. Diabetes mellitus (DM)

Diabetes disease has also seen a large increase in recent years and there are more and more people with impaired glucose tolerance and an increased risk of diabetes. About 537 million people have diabetes and about 316 million people have impaired glucose intolerance and a risk of developing diabetes [22].

Diabetes mellitus is a metabolic disorder, determined by chronic hyperglycemia with the disorder of carbohydrate, fat and protein metabolism, and as a result, there is a lack of insulin, efficacy of its action or tissue insensitivity to the hormone [23]. Insulin is a hormone produced by pancreatic β-cells, and its mode of action is involved in blood glucose control, which allows cells and tissues to convert glucose into energy. If insulin or its action on tissues and cells is absent, it results in a build-up of glucose in the blood and the development of diabetes symptoms [23]. Symptoms are hardly realized because they can be attributed to other reasons, however, some of the symptoms of the most common ones can be weight loss, excessive thirst (polydipsia), excessive urination (polyuria) and dehydration, general fatigue, excessive hunger, problems with vision or blurred vision and vaginal infection. There are several types of diabetes, namely, type 1 diabetes, type 2 diabetes, gestational diabetes mellitus and other types of diabetes associated with other diseases such as pancreatic diseases, monogenic diabetic syndrome, and chemical inducers [23]. Type 1 diabetes (Figure 1) is characterized by a lack of insulin secretion because of pancreatic β-cell degeneration. The body is then forced to utilize fats as an energy source instead of glucose, and there is a production of a toxic by-product, ketones. At the treatment level, patients require daily doses of insulin [23]. Type 2 diabetes (Figure 1) develops because of the progressive loss of insulin-secreting cells or tissue resistance to the hormone, where tissues do not absorb insulin and its action in the body does not occur. This type of diabetes is associated with increased body mass, which is a result of unhealthy eating patterns and lack of exercise [23].

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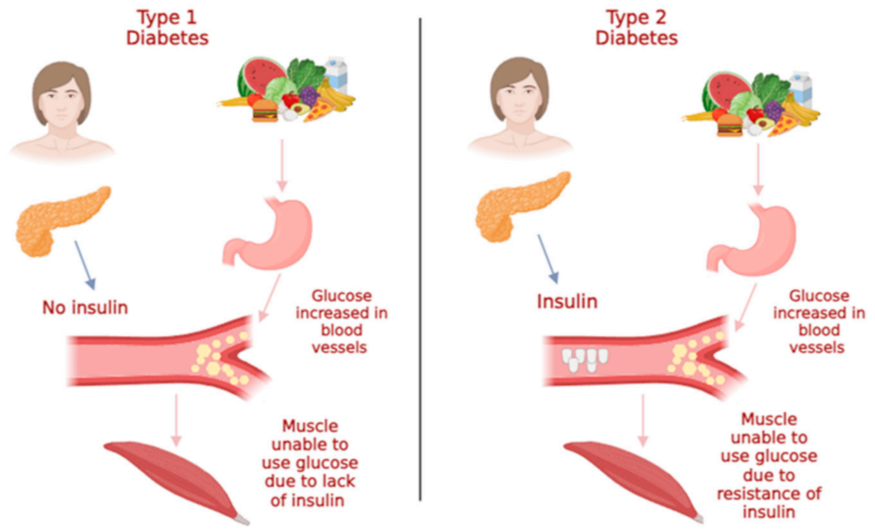

Figure 1. Types of diabetes mellitus and their syndrome.

Type 2 diabetes mellitus (DMT2) is the most common form and accounts for approximately 90% of all diabetes cases [24], being associated with other types of diseases such as high blood pressure (hypertension), chronic high insulin levels (hyperinsulinemia) and abnormal levels of cholesterol, triglycerides and lipids (hyperlipidemia). In addition, abnormalities in lipoproteins are associated with type 2 diabetes, as well as its diagnosis and treatment [23].

Treatment of type 2 diabetes involves stimulating and increasing endogenous insulin production or inhibiting the digestive enzymes α-amylase and α-glucosidase. α-amylase hydrolyses starch at the internal α-1,4-glucosidic bonds and produces linear or branched malt oligosaccharides. The α-glucosidase converts the previously produced oligosaccharides into glucose [23]. In this way, the two enzymes play different but interdependent roles for glucose production to occur, where the first enzyme regulates the rate of starch digestion, and the second enzyme acts in the conversion of sugars. Some synthetic inhibitors of these enzymes are already used, such as sulfonylureas, biguanides, glucose-lowering inhibitors, etc., however, their continuous use is not advised due to problems of flatulence, cramps, vomiting, weight gain and liver function disorders [23]. On the other hand, techniques based on mechanisms of action are also used, such as stimulating insulin production and release, increasing glucose transport activity and decreasing glucose absorption in the gut. However, these types of treatments have low efficacy and side effects [25].

The inclusion of dietary fiber in the diet is associated with benefits in the prevention and reduction of bowel disorders, coronary heart disease and type 2 diabetes [26]. Dietary fibers are classified as non-degraded and non-digestible material in the human body and small intestine. They consist of carbohydrate polymers, present in plant cell walls, such as cellulose, hemicellulose and pectin's, but also polysaccharides such as agar, carrageenan, and alginate, extracted from macroalgae. Classified according to solubility, two types are distinguished, soluble fibers and insoluble fibers, which as the name implies, the first dissolves in water and the second does not. These carbohydrates are found in different foods and have different properties and, increasingly, their beneficial effects have been studied, such as cholesterol reduction, diabetes control with a reduction in blood glucose levels, and better functioning of the digestive system [26]. In addition, this type of fiber also improves the growth and activity of intestinal bacteria, exerting a prebiotic activity.

Diabetes or acute hyperglycemia or chronic is associated with the production of reactive oxygen species (ROS), which activates cell apoptosis. The induction of ROS production is through mitochondrial enzymes of the respiratory chain, namely xanthine oxidases, lipoxygenases, cyclooxygenases, nitric oxide synthases and peroxidases [27]. In different studies associated with diabetes, the imbalance between oxidizing species has already been studied, which as a result caused oxidative stress and cell death, therefore, down-regulation of ROS production may be important in

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controlling diabetes-associated complications [27–29]. Oxidative stress is defined as the imbalance in the production and neutralization of reactive oxygen and nitrogen species [23], and to maintain cellular homeostasis, cells need to balance ROS production and consumption.

Antioxidants are molecules that slow down or prevent oxidation processes, and as a result, there is neutralization and elimination of ROS in the body's cells. These compounds can be obtained from the diet, but there are also commercial synthetic antioxidants, such as butylated hydroxytoluene (BHT), propyl gallate (PG) and butylated hydroxyanisole (BHA), however, they are unstable, can cause side effects and are associated as promoters of carcinogenesis [23,30].

2.3. Cholesterol

The circulation of lipids in the bloodstream, such as cholesterol, occurs through lipoproteins, such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Pancreatic β-cells can synthesize cholesterol, via the mevalonate pathway, and its excess is removed by the reverse cholesterol transport process [31]. There are associations between cholesterol accumulation and pancreatic β-cell dysfunction, with individuals with type 2 diabetes exhibiting lipid abnormalities, which contribute to cholesterol accumulation in the cells and influence insulin secretion [31,32].

Dyslipidemia is characterized by the presence of high levels of lipids in the blood and is usually associated with abnormal glucose metabolism. Both normal lipid parameters, such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), as well as non-traditional parameters, are related to the development of diabetes. Glycemic control is beneficial for lipoprotein levels in diabetes, as there is a reduction in cholesterol and triglycerides through a decrease in LDL and an increase in LDL catabolism [33].

3. Macroalgae

Currently, more than 70 species of algae have been approved for food consumption, with each type having a varied nutrient composition according to the species and abiotic factors such as location, temperature, habitat, etc. [34], and no species is harmful to human health [35].

Marine macroalgae are aquatic, multicellular, macroscopic organisms that, based on thallus color, pigment composition and biochemical aspects can be classified into three groups: Chlorophyta (green algae), Rhodophyta (red algae) and Ochrophyta - Phaeophyceae (brown algae) [36,37]. In certain aquatic ecosystems, algae act as primary producers, as they synthesize organic material and oxygen for the metabolism of consumer organisms [38]. As they are species that live in extreme environments and with variations in the different factors, they need a rapid readaptation to the changes that occur, producing primary metabolites (proteins, amino acids, polysaccharides and fatty acids) that act as stress deterrents, and secondary metabolites (phenolic compounds, pigments, vitamins and other bioactive compounds) as a response to the changes that occur in the environment [39].

Although more research and discovery are still needed on macroalgae, it is already known that the substances that these beings synthesize have great potential in different areas such as pharmaceuticals, food and cosmetics. In the pharmaceutical and cosmetic industry, macroalgae are useful as they are used as a source of natural ingredients or bioactive compounds. They are also used in human food, which is quite prevalent in Asian countries, but they are also used in livestock and agriculture, in animal feed, nutritional additives and stimulants in plant growth [37].

The demand and need for the consumption of non-toxic and environmentally friendly products has increased, and therefore algae have started to be used as a source of natural compounds, also as a replacement for synthetic food additives [37,40]. Compared to other taxonomic groups, macroalgae are rich in biologically active compounds such as polysaccharides, phenolic compounds, proteins, polyphenols and pigments, as well as certain micronutrients such as potassium, sodium, calcium and iron [36]. There is also an interest in nutraceutical preparations as a health benefit, and macroalgae have potential as dietary supplements and their consumption is associated with beneficial health effects due to the components they contain. Bioactive molecules that can be incorporated as a supplement in the diet, can be considered nutraceutical food products [41], and the in vitro biological

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activity of several compounds with antioxidant capacity has already been studied [42,43], anti-inflammatory properties [44], applications in the treatment of Alzheimer's and Parkinson's disease [45], in the control of glycemic index [46] and potential as antidiabetic [47].

In 2015, a set of 193 countries came together to create a plan to improve the health of the planet, where they listed 17 Sustainable Development Goals (SDGs), all interlinked with each other, aiming for a better and more sustainable future. These goals address issues such as poverty, inequality, climate change, environmental degradation, peace and justice [48]. Macroalgae have the potential to address these sustainability challenges as they are a source of food (SDG 2), can provide clean water (SDG 6), green energy (SDG 7) and improve global health (SDG 3), and are a renewable and fast-growing source of biomass [48].

According to the problems mentioned above, macroalgae have the potential to be used in the production of certain foods due to their high content of proteins, amino acids and minerals, which has been shown to increase the nutritional value of different products [49]. On the other hand, the anti-diabetic effect, glycemic index control and cholesterol control have been demonstrated through compounds present in macroalgae, making it possible to develop products with potential in the treatment or improvement of the diseases.

3.1. Proteins

The addition of proteins from different sources, such as animal, vegetable and soya products are widely used in products with a low content of these compounds, however, it becomes an expensive process and there are relationships between the consumption of this type of proteins and certain intestinal diseases [20]. Thus, macroalgae can be a substitute for these sources because such proteins are also found in the composition of these living beings, such as the macroalgae *Saccorhiza polyschides* (Ochrophyta, Phaeophyceae) (Figure 2a) (14%) and species of the genus *Gracilaria* (Rhodophyta) (Figure 2b) [50,51]. Edible seaweed is considered a nutraceutical food, as it has higher protein values than pulses and soya and is therefore increasingly common. In addition, this type of compound present in red algae has demonstrated bioactive properties with pharmaceutical potential [52].

Figure 2. Marine Macroalgae: a - *Saccorhiza polyschides* (Phaeophyceae); b – *Gracilaria* sp. (Rhodophyta). Scale bar = 1 cm.

3.2. Polysaccharides from macroalgae

Hydrocolloids or polysaccharides can be used as gluten substitutes due to the stabilization and texture enhancement, that they provide [20]. These compounds are used as thickening agents, and stabilizers, to improve the quality of the final product and to extend its shelf life [20,53]. These types of molecules are part of the composition of macroalgae and are used for various purposes in food products, such as water retention in meat products, increasing viscosity in soups, broths and beverages, and as gluten substitutes [54]. The addition of algae to gluten-free bakery products favors the polysaccharide network. In studies where different concentrations of macroalgae were added to the dough of gluten-free products, the authors report that the algae interacts with other components present in the dough and contributed to an improvement in the rheological properties of the dough, greater retention of gas (CO_2) that causes an increase in the volume of the dough and the final product [49], therefore, being a good substitute for gluten in the bakery industry.

Brown algae (Ochrophyta, Phaeophyceae) contain alginate and fucoidan, while red algae (Rhodophyta) contain polysaccharides such as agar and carrageenan. Finally, green algae (Chlorophyta) contain cellulose and hemicellulose [55].

Alginate (Figure 3) is extracted from brown macroalgae and consists of linear, unbranched compounds of β-1,4-D-mannuronic acid and α-1,4- L-guluronic acid. These types of polysaccharides are classified as phycocolloids, due to their ability to form colloidal systems in the presence of water. In the presence of metal ions such as calcium, sodium or magnesium, alginic acid reacts with the ions and forms alginate. Calcium alginates are insoluble in water, but with sodium and magnesium ions, these alginates become water-soluble [56].

Alginates are used industrially due to their characteristics as stabilizers, thickeners and emulsifiers, but due to more specific properties, namely gel strength, porosity and biocompatibility, they have been increasingly used as biomaterials in engineering [56].

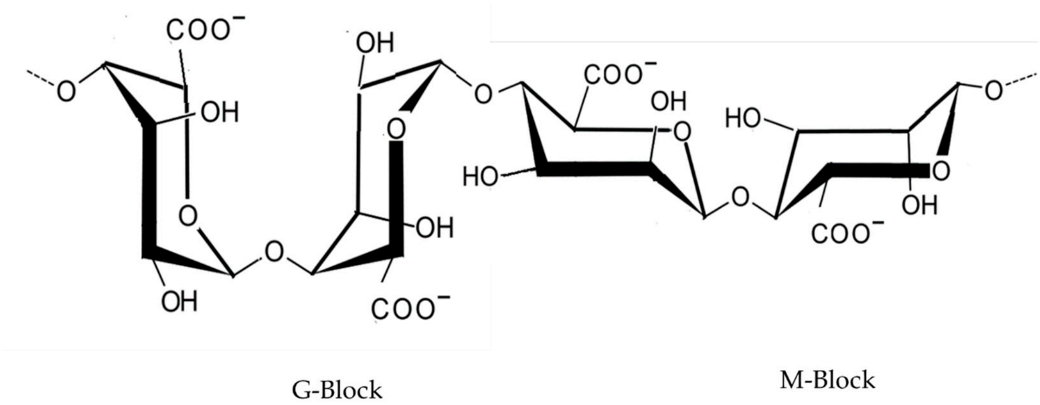

Figure 3. Alginate: Alternating α-1,4-L-guluronic acid (G-Block), and β-1,4-D -mannuronic acid (M-Block).

Fucoidan (Figure 4) is a polysaccharide sulphate, synthesized by brown algae. It mainly contains fucose but may have other types of monomers such as glucose, galactose, xylose and mannose. Depending on the species of macroalgae from which they are extracted, fucoidans may have different lengths of chain, branching structures and sulphate compounds content. This type of polysaccharide can be divided into two subgroups: one group with residues of α-1,3-fucopyranose, and a second group with alternating residual of α-fucopyranose at 1,3 and 1,4 [56].

Fucoidans are important in regulating water retention and ions in algae cell walls, to avoid water loss and osmotic stress in the presence of low tide seasons [56].

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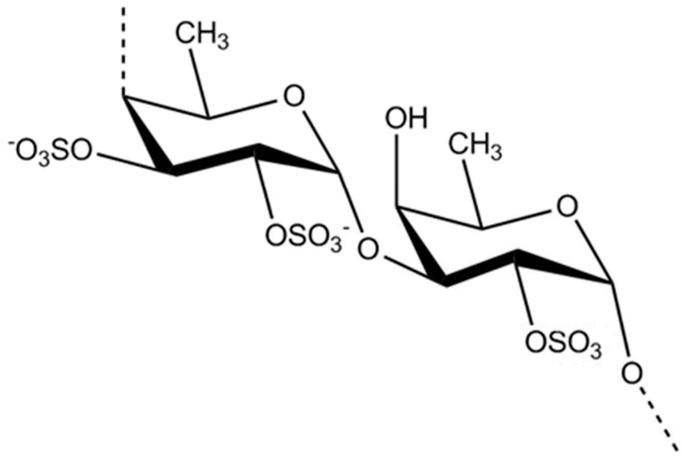

Figure 4. Fucoidan: Alternating 1,3- and 1,4-linked α-L-fucopyranose and α-1,3-L-fucopyranose.

Agar (Figure 5) is a sulphate polysaccharide, present in the cell walls of red macroalgae, such as the genus *Gelidium* and *Gracilaria*. It consists of agarose, a neutral polysaccharide with a linear and repeated structure of agarobiose disaccharides, and of agaropectin, an acidic polysaccharide, composed of sulphate, methyl, pyruvic acid and glucuronic acid [57].

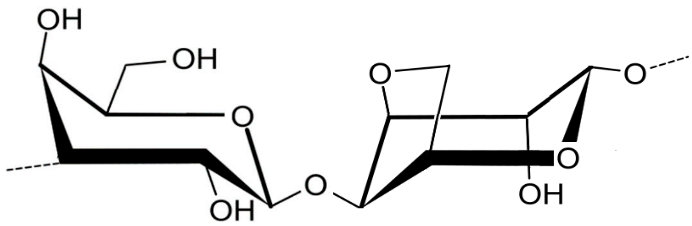

Figure 5. Chemical structure of agar.

Carrageenan (Figure 6) is a sulphate polysaccharide, also present in the cell walls of red macroalgae. It has a high molecular weight and is composed of α-1,3-D-galactopyranosyl and β-1,4-D- glucopyranosyl groups bound to residues of 3,6-anhydrogalactose [58]. The three most important types of carrageenan are kappa (κ), iota (ι) and lambda (λ), which differ in the position of ester sulphate groups and the number of anhydrogalactose. Carrageenan extracted from *Chondrus crispus* (Rhodophyta), can be used as a gelling and thickening agent in gluten-free bakery products. It helps improve the texture and consistency of gluten-free doughs and batters, addressing the challenges associated with gluten replacement while enhancing the nutritional value of the end products [59].

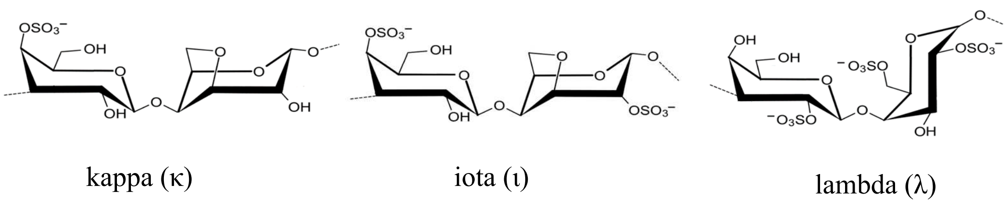

Figure 6. Chemical structure of the three types of carrageenan: kappa, iota and lambda.

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As mentioned earlier, algae produce different polysaccharides, which have already demonstrated their antidiabetic effects. For example, red algae contain sulphate polysaccharides, such as agar and carrageenan, which in various studies [60–62] have already verified the ability to inhibit digestive enzymes, namely α-amylase and α-glucosidase, and as a result there is a reduction in blood glucose levels. This event is quite important in controlling blood glucose peaks after meals and food intake. Specifically, in one study, inhibition of digestive enzymes with *Fucus vesiculosus* (Ochrophyta, Phaeophyceae) (Figure 7) extracts were demonstrated compared to the commercial drug acarbose [63].

Figure 7. *Fucus vesiculosus*. Scale bar = 1 cm.

There is a beneficial effect of the consumption of dietary fibers with certain diseases such as coronary heart disease, type 2 diabetes and some intestinal disorders [26], and in their composition, macroalgae contain this type of compounds, both soluble and insoluble fibers, which can slow down the digestion and absorption of glucose [25]. In addition, fiber contains interesting biological activities such as lowering cholesterol and blood glucose levels [26]. In one study, where obese diabetic individuals ate dried algae, a decrease in glucose concentration and a beneficial change in lipid levels was observed [64].

On the other hand, macroalgae are rich in pigments such as chlorophylls, carotenoids and phycobilins. A pigment present in brown algae, fucoxanthin, stimulated glucose absorption in cells and improved insulin sensitivity. This type of molecule activates the signaling pathways involved in the production and action of insulin, such as the PI3K/Akt pathway, which promotes the absorption of glucose in the cells, contributing to the control of the glycemic index [24].

3.3. Natural antioxidants

Natural antioxidants can remove free radicals and prevent the oxidative stress process. Additionally, natural antioxidants can help increase the life span of certain foods, so consuming these compounds can protect the body and foods against this type of process [23,65]. In studies, the positive and beneficial health effect of natural antioxidants has been observed, namely, in the prevention of cardiovascular disorders, some types of cancer and in the control of diabetes and organ protection [66,67]. The most well-known natural antioxidants are ascorbic acid, carotenoids, flavonoids and polyphenols, glutathione, phlorotannin and alkaloids, and most can be produced and found in plants and algae [23].

Macroalgae contain high concentrations of phenolic compounds, being one of the largest sources of natural antioxidants. Phenolic compounds are made up of a benzene ring structure that binds to hydroxyl groups [68], which removes metal ions, such as Cu and Fe, through chelation processes [69]. In several studies the antioxidant activity of macroalgae extracts has been tested, obtaining promising results and a great potential for ROS removal [62,68,70,71]. It has also been studied the antioxidant effect of polysaccharides extracted from macroalgae, which can contribute to the removal of reactive

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species of oxygen, associated with diabetes [24]. Hyperglycemia that occurs in diabetes promotes the production of oxidative species of oxygen (ROS), contributing to oxidational stress and inflammation. Thus, natural compounds present in macroalgae have important biological activities in neutralizing ROS, helping in the control of cellular damage, as well as in other processes involved in diabetes [24].

3.4. Cholesterol

Cholesterol is important to cell structure and enters various metabolic pathways, and regulation of this compound is important for normal lipid metabolism. Deregulation of cholesterol in the body is associated with various metabolic diseases, such as type 2 diabetes, heart disease and liver disease [72]. Phytochemicals have beneficial effects in reducing cholesterol levels by inhibiting the expression of enzymes and transcription factors associated with metabolism. Phytochemicals are secondary metabolites synthesized naturally in microalgae or macroalgae, for example [72], and include carotenoids, sterols, and polysaccharides. In some studies, they used hazardous algae extracts in phytochemicals as a dietary supplement, and observed a reduction in total cholesterol, triglycerides and LDL levels [73–75]. On the other hand, compounds present in macroalgae such as polysaccharides, antioxidants such as fucoxanthin, and phenolic compounds have also been shown to reduce cholesterol levels [76–80].

4. Algae Food Products as healthcare solution

Algae demonstrate potential for its use in food products, such as bread, and its effects have been studied in several studies. The fact that they have a high content of minerals, proteins and amino acids can provide a higher nutritional value compared to conventional foods [49]. Studies addressing the effect of adding certain macroalgae to pasta or flour in bread production are still scarce. The first to conduct studies of this type were Medvedeva et al. [81], who examined how the use of algae products can increase the nutritional value of bread. Mamat et al. [82] verified the rheological properties in the bread paste and the quality of the same, after adding seaweed to the flour. It is also already known the beneficial effects that bioactive compounds, present in macroalgae, can present in different metabolic diseases. Allsopp et al. [83] enriched bread with red algae, and evaluated, in a study with humans, how its intake can influence markers of inflammation, lipid profile, thyroid function and antioxidant capacity. The studies mentioned above mainly refer to wheat bread, however, studies where algae are added to gluten-free bread are even more scarce. Różyło et al. [49], evaluated the influence of adding brown macroalgae on the properties of gluten-free bread, namely, physical and sensory properties and antioxidant capacity, having obtained promising results in the production of this type of bread. Within products that do not contain gluten, gluten-free pasta has already been developed with the addition of algae to rice flour, resulting in a reduction in energy value, increased protein content, as well as insoluble dietary fiber [84]. Studies where there is the evaluation of different factors, such as the influence of macroalgae compounds in the production of gluten-free bread and possible treatments of diabetes and the reduction of cholesterol through the properties of the bioactive compound, are not found in the literature, so they are strategies and factors interesting to study so that foods or nutraceutical preparations based on macroalgae can be produced.

In light of the aforementioned challenges, certain macroalgae species, such as *Ascophyllum nodosum* (Figure 8) and *Fucus vesiculosus* (Phaeophyceae), *Cladophora* spp., and *Ulva* spp. (Chlorophyta) present a promising avenue for the development of specialized foods owing to their abundant reservoirs of proteins, amino acids, and minerals. Studies, such as the one conducted by Różyło et al. [49] Menezes et al. in 2015 [85], have indicated that incorporating these macroalgae species into food formulations can significantly elevate the nutritional value of various products. This becomes particularly crucial when addressing the limitations of gluten-free items in the bakery industry, as macroalgae-based additives may help compensate for the loss of gluten's beneficial characteristics.

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Figure 8. *Ascophyllum nodosum.* Scale bar = 1 cm.

Beyond enhancing nutritional profiles, *A. nodosum* and *F. vesiculosus* offer a multifaceted approach in managing coeliac disease and diabetes. Their bioactive compounds, such as sulphated polysaccharides, have demonstrated impressive anti-diabetic effects, which include controlling glycemic index levels and mitigating the adverse effects of hyperglycemia. Moreover, these seaweed-derived compounds show promise in effectively regulating cholesterol levels, thereby reducing the risk of related health complications [86].

By harnessing the inherent potential of *A. nodosum* and *F. vesiculosus*, it becomes feasible to develop innovative food products that can serve as therapeutic interventions or improvements for individuals with coeliac disease and diabetes. Such products may not only cater to the dietary needs of these specific populations but also provide added health benefits through the incorporation of these specific macroalgae-derived bioactive nutraceuticals. As research in this field continues to unfold, with a focus on exploring other macroalgae species as well, it is anticipated that macroalgae-based foods will emerge as a valuable adjunct to conventional treatments, contributing to a more comprehensive and effective approach to managing these diseases and improving the overall well-being of affected individuals [87].

Porphyra/*Pyropia* (Rhodophyta) (Figure 9), commonly known as Nori, is a red alga rich in protein, vitamins, and minerals. It can be incorporated into gluten-free snacks or crackers, providing a source of essential nutrients for individuals with coeliac disease while also offering a low-carbohydrate option for those managing diabetes or hyperglycemia [88].

Figure 9. *Porphyra umbilicalis*. Scale bar = 1 cm.

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Palmaria palmata (Rhodophyta) (Figure 10), also known as Dulse, is a red algae species with antioxidant properties. Its powdered form can be included in gluten-free baking mixes, offering both nutritional benefits and contributing to the control of oxidative stress associated with diabetes [89]. On the other hand, these red algae contain high levels of protein, between 9 and 25 per cent, which in bread production has been shown to increase the nutritional profile of bread, which is accepted by consumers and has the potential to be developed as a bioactive product [90].

Figure 10. *Palmaria palmata*. Scale bar = 1 cm.

Brown macroalgae show a high concentration of secondary metabolites, which have shown antidiabetic activity in vivo, and studies have seen a reduction in blood glucose, triglycerides and cholesterol levels, as well as hepatoprotective activity [91,92]. In studies with diabetic rats, a decrease in glucose levels, weight loss, and normalization of triglyceride and cholesterol levels were observed. A healing effect and regeneration of pancreatic cells were also observed in induced diabetic rats after administration with different concentrations of algae extracts [93,94].

Saccorhiza polyschides, initially classified as *Fucus polyschides*, is considered an edible species and has therefore been studied for future nutraceutical applications [95]. Is a brown alga (Phaeophyceae), belonging to the family Phyllariaceae, and the class Phaeophyceae [50,96]. This alga is opportunistic and is most abundant in southern Europe, where it colonizes rocky substrates in the sublittoral [50]. Its sporophyte is pale dark brown, with differentiated blades and a twisted base, and the attachment zone is composed of a rough "bulb". It is a monocarpic and annual alga, but it is fast growing and can reach between 2 and 4 meters in length in just 2 months [50,96]. It is a species that contains a high percentage of carbohydrates (45.6%), protein (14.4%), low levels of lipids (1.1%) and a concentration of minerals higher than that found in terrestrial plants. Due to its ability to adapt to environmental changes, such as salinity and temperature, it contains [95] bioactive compounds synthesized in the presence of these types of changes [50].

Certain species of *Gelidium* (Rhodophyta) can produce extracts rich in bioactive compounds, including anti-diabetic agents. These extracts can be incorporated into functional beverages or health supplements targeting glycemic index control and diabetes management [97].

Gracilaria species have been studied for their ability to reduce cholesterol levels. Incorporating *Gracilaria* extracts into food products, such as gluten-free pasta or spreads, could help support individuals with coeliac disease and diabetes while addressing cholesterol-related health concerns [88,98]. The genus *Gracilaria* contains more than 300 species and 160 are taxonomically accepted [99]. It is of great economic importance as it has high biomass yields and the ability to produce agar. The species of the genus *Gracilaria* produce weaker gels compared to other macroalgae genera, however, they are considered one of the most important sources of agar because they are fast-growing algae with a relatively low acquisition cost [38,99]. The addition of polysaccharides, extracted from this type of algae, has been shown to improve the nutritional, structural, and shelf-life characteristics of foods. These species have low lipid content and contain docosahexaenoic acid (DHA), a polyunsaturated fatty acid that is important in reducing the risk of cardiovascular diseases. In terms of amino acids, the most abundant are aspartic acid, alanine, glutamic acid and glutamine, but they are also a good source of soluble and insoluble dietary fibers and are therefore good alternatives to cereal-based fibers, which are used in Western countries [51].

It's important to note that the utilization of red algae species in food products requires careful research and formulation to ensure safety and effectiveness. Additionally, individuals with allergies or sensitivities to seafood should be cautious when consuming products containing seaweed or algae-derived ingredients [12,100].

5. Conclusions

The exploration of seaweed superfoods as bioactive nutraceuticals presents a promising and multifaceted approach to address the nutritional challenges and health needs of individuals with coeliac disease, diabetes, and hyperglycemia. Through the utilization of macroalgae, such as *Ascophyllum nodosum*, *Fucus vesiculosus*, and various red algae species like *Chondrus crispus*, *Porphyra*, *Palmaria palmata*, *Gelidium*, and *Gracilaria*, innovative food products can be developed with enhanced nutritional content and functional properties. These seaweed-based formulations have shown potential in compensating for the loss of gluten's characteristics in gluten-free products, controlling glycemic index levels, managing oxidative stress, and regulating cholesterol, thus offering valuable support to individuals with coeliac disease, diabetes, and hyperglycemia. As research in this field progresses, it is envisaged that seaweed superfoods will continue to play a vital role in fostering improved dietary interventions and contributing to the overall well-being of those affected by these conditions.

Author Contributions: Writing—original draft preparation, J.O.T., J.C. and L.P.; writing—review and editing, J.O.T., J.C. and L.P.; visualization, A.V.; supervision, L.P. and A.V. All authors have read and agreed to the published version of the manuscript. The work as also supported by IATV (Instituto do Ambiente, Tecnologia e Vida)

Funding: Please add: This work was financed by national funds through the FCT—Foundation for Science and Technology, I.P., within the scope of the project LA/P/0069/2020 granted to the Associate Laboratory ARNET, UIDB/04292/2020 granted to MARE—Marine and Environmental Sciences Centre.

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable

Data Availability Statement: Not applicable

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

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