

# Algae and Type-2 Diabetes Mellitus

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Type-2 diabetes mellitus (T2DM) is a major systemic disease which involves impaired pancreatic function and currently affects half a billion people worldwide. Diet is considered the cornerstone to reduce incidence and prevalence of this disease. Algae contains fiber, polyphenols,  $\omega$ -3 PUFAs, and bioactive molecules with potential antidiabetic activity.

Keywords: algae ; diabetes ; functional food ; functional meat ; microbiota ; metabolism

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## 1. Introduction

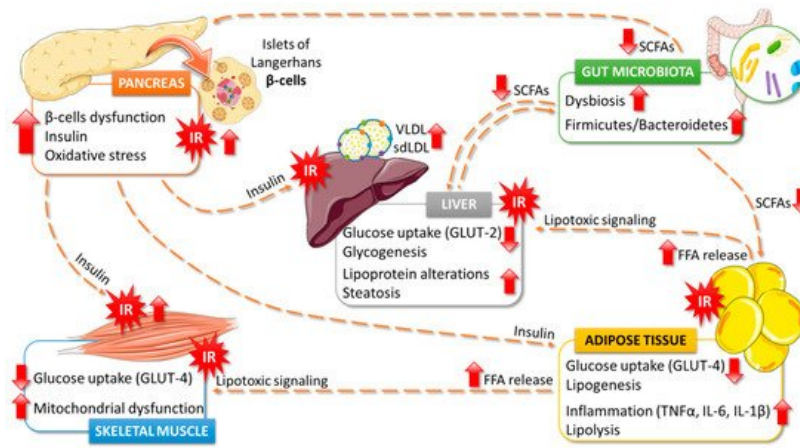
Type-2 diabetes mellitus (T2DM) is a metabolic disorder characterized by an imbalance in blood glucose level and an altered lipid profile. The study of T2DM has become a priority, given its high prevalence (around 90% of diabetes mellitus cases in worldwide) and complexity <sup>[1]</sup>. Among the factors intervening in the development of T2DM, lifestyle, diet (high-fat, high sugar, and high-energy consumption), obesity, gut microbiota (GM), and genetics are important contributors of the pathology development <sup>[2][3][4][5]</sup>.

Related to dietary habits, globalization has conditioned changes in food intake, with algae consumption, either as a food or as dietary supplement, being increasingly frequent in western countries <sup>[6][7][8]</sup>. Algae contain a variety of nutrients and phytochemicals that exhibit various biological activities <sup>[9][10]</sup>. Algae-rich diets traditionally eaten by Asians has consistently been related to a lower incidence of chronic diseases such as cancer, cardiovascular, and heart disease <sup>[11][12]</sup>. There is a very active line of research studying the modulation of nutrients and bioactive components on gene expression, a science known as nutrigenomics. In addition, the components of the diet can modulate epigenome producing permanent changes in gene expression, and metagenomics referring to the modulation of the microbiota <sup>[13][14][15]</sup>. Recent studies have shown that, besides genetic predisposition and diet, the GM affects glucose and lipid metabolisms as well as influences the balance between proinflammatory and anti-inflammatory effectors in the liver, affecting T2DM <sup>[16][17]</sup>. Given the richness of algae in bioactive compounds, it is a very promising component in these new areas of research.

Nowadays, there is a high interest in healthy natural products, including algae, which could prevent the appearance of T2DM and its comorbidities <sup>[18]</sup>. In fact, algae and their bioactive compounds are added as ingredients of functional foods (term coined for such foods with potential health benefits) <sup>[19][20]</sup>. A regular consumption of functional foods appears to be associated with improved antioxidant enzymes, suppress over production of proinflammatory cytokines, insulin sensitivity, and hypocholesterolemia functions, which are considered essential to preventing and controlling T2DM <sup>[20][21]</sup>. There have been indications that algae could be used as antidiabetic foods/ingredients, but the mechanisms of action remain unclear. Likewise, it is important to differentiate between including a whole alga or an extract, because the extraction process determines the subsequent activity observed, or their isolated compounds <sup>[22][23]</sup>. Despite their potential health benefits, recent controversy exists about the utility of algae as some adverse events have been associated with their consumption. Biochemical characteristics of the cell wall of algae, rich in polysaccharides and proteins with anionic carboxyl, sulfate, and phosphate groups, make them important bio sorbents of toxic heavy metals (As, Pb, Cd, etc.) from industrial wastewater. In addition, certain seaweeds can present dangerously high concentrations of iodine <sup>[24][25][26]</sup>.

## 2. Type-2 Diabetes Mellitus

T2DM pathophysiology is due to a progressive loss of adequate  $\beta$ -cell insulin secretion frequently on the background of insulin resistance (IR) by tissues such as skeletal muscle, liver, and adipose tissues (Figure 1) <sup>[27]</sup>. T2DM is clinically diagnosed by the presence of hyperglycemia, increasing the risk of developing chronic complications, which are due to complex and interconnected mechanisms between hyperglycemia, IR, low-grade inflammation, and accelerated atherogenesis <sup>[28]</sup>.



**Figure 1.** Representative scheme of the Type-2 diabetes mellitus pathophysiology. Main organs affected in T2DM and their interrelation in insulin resistance development. FFA, free fatty acids; GLUT-2, type 2 glucose transporter; GLUT-4, type 4 glucose transporter; IL-1 $\beta$ , interleukin 1  $\beta$ ; IL-6, interleukin 6; IR, insulin resistance; sdLDL, small dense low density lipoproteins; SCFAs, short-chain fatty acids; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; VLDL, very low density lipoproteins.

Metabolic imbalances linked with IR are based on the outcome of metabolic function of insulin on carbohydrate, fat, and protein. Under normal conditions, glucose uptake by peripheral tissues occurs through the InsR/IRS/PI3K/AKT pathway, whose defective activity is responsible for IR. Briefly, when insulin reaches the target cell, it binds to an insulin receptor (InsR), which autophosphorylates and induces insulin receptor substrate (IRS) activation. This conformational change allows the binding of phosphatidylinositol 3-kinase (PI3K) through its SH2 domain, whose activation promotes the PI3,4,5-trisphosphate (PIP3) formation in the plasma membrane. PIP3 serves as a binding site for AKT, a membrane-displaced protein that is phosphorylated at residues Ser<sup>473</sup> and Thr<sup>308</sup>. AKT is a major contributor in insulin signaling, whose phosphorylation enables the translocation of the type 4 glucose transporter (GLUT 4) to the plasma membrane and regulates glycogen synthesis through glycogen synthase kinase-3 (GSK3) and glycogen synthase (GS) [29][30]. If the disease continues to progress, the  $\beta$ -cells degenerate and insulin production is reduced, leading to less glucose uptake at the tissue level and greater production and release of that substrate at the liver, reaching a vicious cycle that worsens the imbalance in glucose metabolism until it leads to T2DM.

Dyslipidemia is a cluster of serum lipids and lipoproteins alterations highly prevalent in T2DM patients and characteristics of metabolic syndrome (MS) [31][32]. This T2DM dyslipidemia cluster implies elevated levels of triglycerides (TG) as large very-low-density lipoproteins (VLDL1), low high density lipoprotein cholesterol (HDL-C) levels and raised amounts of dense and small low-density lipoproteins (LDL). Together, these alterations are known as “the atherogenic lipid triad” [33]. This lipid triad is associated with IR, central obesity, and non-alcoholic fatty liver disease (NAFLD) and relates to excessive flux of free fatty acids (FFA) from visceral adipose tissue that also contributes to IR and VLDL1 formation. VLDL1 particles are more exposed to the cholesterol ester transfer complex (CETP) that metabolically helps form TG rich in high-density lipoprotein (HDL) and small, dense LDL [34][35]. The increase of plasma TG drives the changes of core lipids between TG rich lipoproteins (TRLs) and HDL particles. There is a transfer increase of cholesterol ester and TG between HDL and TRLs by means of CETP, resulting in the triglycerides enrichment of the latter. HDL-TG are good substrates for hepatic lipase and the hydrolysis produces smaller HDL particles. The catabolic rate of the small HDL, is faster than that of normal HDL, resulting in a reduced amount of circulating HDL particles [33]. Differing from normal situations, IR reduces lipoprotein lipase (LPL) activity giving rise to prolonged VLDL half-life but increases hepatic lipase activity that enhances HDL enriched TGs catabolism originating from small and dense HDL particles, with little antioxidant power and a shorter half-life. The lipid changes associated with T2DM are attributed to increased FFA flux secondary to IR and aggravated by increased inflammatory adipokines [36].

High TG and low HDL-C levels with the TG/HDL-C ratio are parameters normally considered to diagnose T2DM, suggesting the importance of lipoprotein metabolism in this pathology [37][38]. In addition, Apo-B100 availability is increased in IR contributing to the small LDL particle. As these particles are depleted in cholesterol, determining LDL-C in T2DM has little diagnostic value [33].

T2DM development depends on various genetic, environmental, socioeconomic, and lifestyle factors [39]. Genetic charge plays a vital role in this disease, thus, individuals with diabetic first-degree relatives are four to six times more likely to develop T2DM. Although several genes participate in the physiopathology of T2DM, some gene variants play an outstanding role on T2DM, like the insulin receptor substrates (IRS1 and IRS2), those for the  $\beta$ -adrenergic receptor (ADRB2 and ADRB3), those for uncoupling proteins (UCP2 and UCP3), and those for the receptor activated by

peroxisome proliferator-activated receptor alpha (PPAR- $\gamma$ ) [40]. Nonetheless, FTO, apoC3, ApoA4, and ApoA5 polymorphisms among others, appear related to the lipoprotein alterations observed in T2DM [41][42].

In relation to lifestyle, T2DM and its associated complications can be prevented or delayed through regular food intake and physical activity. In these sections the role of some nutrients and bioactive components should be discussed with special mention of algal components, which can be considered functional as they could improve glycemic control, activation of antioxidant enzymes, GM, and reduce over production of proinflammatory cytokines during T2DM [43].

### 3. Algae

#### 3.1. Algae Definition and Classification

Algae are not considered a phylogenetic concept, but are a loose set of significant organisms, which have different origins, evolutionary lines, and biochemistry; also may have any or all of these characteristics making them groupable: simple, photosynthetic, aquatic vegetative structures without a vascular system, and reproductive bodies lacking a sterile layer of protective cells [44]. Like plants, they use energy from sunlight, they are present in both fresh and salt waters [44][45], both prokaryotes and eukaryotic taxa are included, and there is a wide range of vegetative morphologies varying in size. In addition, the divisions are distinguished from each other based on characteristics including photosynthetic pigments, starch like reserve products, cell covering, and other aspects of cellular organization [44][46] (Table 1).

**Table 1.** Main characteristics of macroalgal division \*.

Division/Common Name	Specie	Pigments	Storage Product	Cell Structural Wall	Intercellular Mucilage
Phaeophyta/Brown algae	<i>Sargassum polycystum</i>				
	<i>Himanthalia elongata</i>				
	<i>Undaria pinnatifida</i>	Chlorophyll a, c Fucoxanthins	Laminarans	Cellulose,	Alginate acid/Alginates,
	<i>Laminaria spp.</i>	$\beta$ -carotenes Xanthophylls	Mannitol	Chitin	Sulfated polysaccharides (Fucoidans)
	<i>Laminaria japonica</i> , <i>L. digitata</i>				
	<i>Hizikia fusiforme</i>				

Division/Common Name	Specie	Pigments	Storage Product	Cell Structural Wall	Intercellular Mucilage
Chlorophyta/Green algae	<i>Ulva spp.</i>				
	<i>Ulva lactuta</i>				
	<i>Ulva pertusa</i>	Chlorophyll a, b Xanthophylls	Starch	Cellulose, Xylans, Mannans	Sulfated polysaccharides
	<i>Enteromorpha spp. (E. compressa)</i>				
Rhodophyta/Red algae	<i>Pyropia spp.</i>				
	<i>Pyropia tenera</i>	Phycoerythrin			
	<i>Pyropia yezoensis</i>	Phycocyanin Chlorophyll a $\beta$ -carotene	Florideans Starch	Cellulose, Xylans, Mannans	Sulfated polysaccharides (Agar, Carrageenans, Porphyrans)
	<i>Chondrus crispu</i>	Xanthophylls			
	<i>Gracilaria verrucosa</i>				

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Depending on its sizes, algae can be classified as unicellular or colonial microalgae, or multicellular marine organisms (macrophytes seaweeds).

Macroalgae are typically classified based on their chemical and morphological characteristics and mainly based on the specific pigments part of its composition. Thus, they are grouped into one of the three alga divisions: brown algae (also known as kelp. Phylum Ochrophyta, class Phaeophyceae), red algae (phylum Rhodophyta, class Rhodophyceae), and green algae (phylum Chlorophyta, classes Bryopsidophyceae, Chlorophyceae, Dasycladophyceae, Prasinophyceae, and Ulvophyceae) <sup>[47]</sup>. The brown or yellow-brown color of the brown algae is due to fucoxanthin; red algae often have brilliant color due to phycoerythrin and phycocyanin, which are dominant over the other pigments, chlorophyll a,  $\beta$ -carotene and several xanthophylls; green algae contain chlorophyll a and b and various characteristics xanthophylls <sup>[46][47]</sup>.

However, classification of microalgae according to their pigments allows to distinguish between red microalgae (Rhodophyta) which most representatives belong to the genus *Porphyridium*. Green microalgae (Chlorophyta) such as Chlorella (genus *Chlorella*), and Cyanobacteria microalgae that are also called blue-green algae, may be considered seaweed, however, they evolved differently from macroalga. Among them, the microscopic forms of phylum Cyanophyta (Cyanophyceae) stand out, especially the genus *Arthospira* (Spirulina) and *Nostoc* <sup>[48]</sup>.

### 3.2. Algal Consumption and Commercial Importance

Algae have been part of the human diet for thousands of years, based on archaeological evidence <sup>[49]</sup>. Seaweeds have long been traditionally used for food in certain Asian regions (traditionally in China, Japan, and the Republic of Korea) in soups or it used to wrap sushi (Nori)—a practice now spreading to other countries. It has also traditionally been consumed in European coastal communities (for example, in France, Norway, Wales, and Ireland) <sup>[50]</sup>. The demand for edible seaweed is increasing in community markets and new production models and new market trends are emerging <sup>[50]</sup>;

further, it is found in restaurants and on supermarket shelves in many non-Asian countries. Consumers are incorporating recipes based on “seaweed” increasing its acceptance and popularity thanks to its high content of proteins, and minerals and because they are considered healthy and natural <sup>[18][50]</sup>. For example, the direct consumption of brown algae as a human food dates back years and continues today as a valuable food ingredient <sup>[51][52]</sup>.

Due to the high nutritional and pharmaceutical values, seaweeds are traditionally consumed as food or as herbal medicines, along with many other uses; thus, about 221 species of seaweed are of commercial value. In China, algae cultivation is intensive because of its high consumption as food. Over 70 edible species have been reported in the Chinese diet, but only a selection of these are approved for food in the European Union or its Member States <sup>[18][46]</sup>. In addition, the current range of uses of algae has caused their growing cultivation, for example compounds derived from algae (in cosmetics and food) are on the rise <sup>[18][46]</sup>. In Europe, the most exploited algae species are *Laminaria hyperborea*, *Laminaria digitata*, and *Ascophyllum nodosum*. Spain, Portugal, and Germany are the major providers of algae fit for human consumption within Europe. With algae fit for human consumption, the main non-EU suppliers are Chile (approximately 2500 tons in 2015) and China (800 tons) <sup>[48][50]</sup>. Microalgae (*Spirulina* spp.) is also cultivated, although it is much under-reported. Australia, India, Israel, and Japan are among the producers of *Spirulina* <sup>[48]</sup>.

The world production of aquatic plants reached 32.9 million tons in 2017. Farmed aquatic plants included mostly seaweeds (40 aquatic algae) and a much smaller production volume of microalgae (89.000 tons of farmed microalgae) <sup>[53]</sup>. About 31 million tons of seaweeds and other algae were harvested globally for direct consumption (for example: kelps, *Undaria pinnatifida* (Wakame), *Pyropia* spp. (note: some seaweed classified as genus *Porphyra* are now classified as genus *Pyropia*), and *Caulerpa* spp.) or further processing like raw material for the extraction of carrageenan (*Kappaphycus alvarezii* and *Eucheuma* spp.) <sup>[49][53]</sup>. In 2016, China and Indonesia stood out as major producers of aquatic plants. The most widely cultivated species include Japanese Kelp or Konbu (*Laminaria japonica*), *Eucheuma* seaweeds, Elkhorn sea moss (*Kappaphycus alvarezii*), *U. pinnatifida*, *Gracilaria* spp., and Nori (*Pyropia species*) all of them cultivated mainly for nutritional purposes <sup>[53]</sup>. With the cultivation of microalgae, *Spirulina* spp., *Chlorella* spp., *Haematococcus pluvialis*, and *Nannochloropsis* spp., are being marketed for production of human nutrition supplements and other uses <sup>[53]</sup>.

The composition of seaweeds is highly variable, depending not only on the species but also on the time of its collection and their habitat <sup>[53]</sup>. These differences in the composition and concentration of the bioactive compounds present in the different species of seaweed seem responsible for the potential health benefits <sup>[11][54]</sup>. Algal bioactive compounds of commercial interest are not present in terrestrial food sources, include pigments, lipids, polyunsaturated fatty acids (PUFAs), different proteins (lectins, phycobiliproteins, peptides, and amino acids), polysaccharides, sterols, and polyphenols <sup>[11]</sup>. The biological activities reported for these components are varied <sup>[46][47]</sup>. Nonetheless, the presence, form, and level of bioactive compounds of natural algal populations are further influenced by many factors like temporal changes and reproductive development <sup>[55]</sup>.

### 3.3. Algae as Functional Foods or as a Potential Raw Material for Bioactive Ingredients

Preventive and therapeutic approaches to T2DM focus on a holistic strategy that includes promoting a balanced diet combined with pharmacological intervention to reduce/control hyperglycemia, obesity, and cardiovascular complications <sup>[56]</sup>. Prevalence of obesity in developed countries causes greater research and design of new ways to treat pathologies involved such as T2DM, cardiovascular disease (CVD) and hypertension <sup>[57]</sup>. Therefore, the relationship between diet and health has become an important target that allows preventing, or even treating, some of these diseases. Functional foods or ingredients are one of the easiest ways to achieve reduced symptoms, even in T2DM <sup>[43]</sup>. Thus, several products have been reformulated with bioactive compounds or ingredients (e.g., algae have been incorporated in some food matrices, like meat products, to obtain functional meat), in which seaweeds provide a wide variety of positive health characteristics <sup>[58]</sup>.

Due to their technological, organoleptic, and nutritional properties, algae are ideal to be added to many foods to increase their protein and other nutritional contents (salad dressings, beverages, and baked goods) and/or sold as protein supplements <sup>[49]</sup>. In fact, there are several studies that treat the application of algae as functional foods, with interesting conclusive data, in relation to associated comorbidities and CVD, but new studies presented expand their application in the treatment of T2DM, hence, the interest of a review of the latest data in relation to this pathology, their comorbidities, and algae. In addition, protector mechanisms of algae consumption against T2DM remains poorly understood, thus they will be also reviewed. Advance in understanding the role of specific foods as algae, their nutrients and bioactive compounds in the pathogenesis of T2DM is of supreme importance.

Evidence is documented on the critical role of the GM in regulating liver function and development of obese-related metabolic diseases, such as T2DM, IR, and hyperlipidemia. Therefore, the potential of therapies directed at the GM in these diseases is important. Among the different ways that exist to manipulate the intestinal microbiota, active components of algae are included [59]. However, to the best of our knowledge, no previous review has extended the scope and included its effect on GM. The potential of manipulating the GM in this metabolic disorder is assessed, with an examination of the latest and most relevant evidence relating to seaweeds.

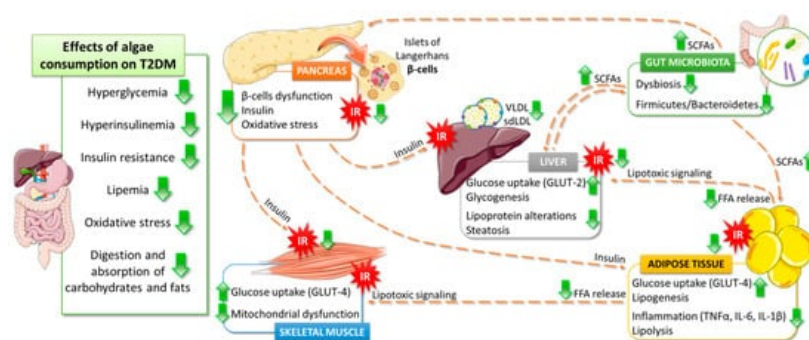
Considering that an integrated approach including multiple biomarkers, genetic variability, effect of GM, and risk/benefit assessment should support the potential health effects of functional foods [60]. This review aims to study the potential preventive or therapeutic action of algae extracts or their isolated compounds against T2DM. In this narrative review, we summarize the evidence from the latest studies on evaluating the effect of the consumption of algae, its nutrients and non-nutrients on the control and management of T2DM, as well as its complications. We also discuss mechanisms and the possibility of using algae as functional foods or nutraceuticals. In addition, scientific experiments performed on seaweed used as functional food are presented.

## 4. Algal Composition, Structure, and Beneficial Effects on Type-2 Diabetes Mellitus

Diet quality and a healthy lifestyle are recommended for the prevention of most chronic degenerative diseases. As already mentioned, T2DM is a metabolic condition characterized by chronic hyperglycemia and results from the interplay of nutritional, environmental, and genetic factors [39]. The role of dietary energy, macronutrients, micronutrients, and bioactive compounds in developing T2DM have been widely studied [61][62]. Epidemiological studies have shown that western diets, rich in saturated fatty acids (SFA) and poor in fiber, are associated with increased risk of chronic diseases such as T2DM [63][64], whereas high intakes of carbohydrate and protein, especially animal protein, enhance the risk for T2DM [65].

## 5. Effects of Algae Consumption on T2DM Pathophysiology

Main positive effects of algae consumption on T2DM pathophysiology are detailed in the following subsections and summarize in Figure 2.



**Figure 2.** Effects of algae consumption on type 2 Diabetes Mellitus pathophysiology. Schematic representation of how algae consumption is able to modulate the different organs affected in T2DM. FFA, free fatty acids; GLUT-2, type-2 glucose transporter; GLUT-4, type 4 glucose transporter; IL-1 $\beta$ , interleukin 1  $\beta$ ; IL-6, interleukin 6; IR, insulin resistance; sLDL, small dense low density lipoproteins; SCFAs, short-chain fatty acids; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; VLDL, very low density lipoproteins.

### 5.1. Glucose Homeostasis

Dietary fiber and polyphenols are among the most widely studied algal compounds for controlling glucose homeostasis. In fact, current studies associate dietary fiber and polyphenols consumption with prevention and management of T2DM. Seaweeds contribute to the daily diet in Korea and Japan, and there is substantial evidence of dietary consumption of different algae and derived food products being associated with low incidence of T2DM in humans [49][66][67][68]. Takahashi et al. [69] studied vegetables that include algae, and observed a significant decrease of HbA1c levels in patients with a daily total vegetable intake of 150 g or more. Furthermore, there was a significant decrease of serum TG levels in patients with a total vegetable intake of 200 g or more. Sometimes, they were linked with improved insulin regulation and sensitivity in human subjects, e.g., *A. nodosum* and *F. vesiculosus* [70], or with a reduction of postprandial glucose concentration and insulin levels, e.g., *U. pinnatifida* [71]. Compound isolates from algae, such as alginates, suppress satiety and to some extent energy intake in most animal and human studies reviewed by Jensen et al. [72]; although it depends

on the vehicle applied for alginate supplementation. Furthermore, only one long-term intervention trial found effects on weight loss. Further, Tanemura et al. [73] found that the consumption of mekabu (70 g), the sporophylls of *U. pinnatifida*, consumed with white rice for breakfast reduced postprandial glucose in healthy subjects. These results are consistent with those observed by Yoshinaga et al. [74] which show that Wakame intake combined with 200 g of white rice significantly reduced the postprandial blood glucose response. This specific hypoglycemic effect of these algae could be considered as functional food because could reduce the risk for T2DM in human. However, Kim et al. [74] indicate that *A. nodosum* is more suitable than *F. vesiculosus* as a source of fucoidan to inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase activities (enzymes involved in increasing postprandial blood glucose), thus, it is important to investigate the inhibitory enzymatic capacity of each alga. In addition to the preferred algal source, it seems necessary to determine aspect such as time of harvest, extracts from the same species, and doses of treatment because as pointed out in some studies, because they can condition beneficial effects [75][76]. In a specific single blind crossover trial on whole algae, Hall et al. [77] found that adding *A. nodosum* (4%) to bread products decreased the energy intake (16.4%) after a meal in overweight men, whereas no differences were registered in the blood glucose and cholesterol plasma levels.

## 5.2. Lipids Metabolism

As previously commented, the atherogenic lipid triad is a major characteristic of T2DM and it is intimately related to IR [33][78]. Thus, major goals for ameliorating the lipemic triad are to reduce central obesity and IR [79], that would help to normalize the TG and HDL-C values; and the LDL characteristics and/or size. Four main interventions have been reported to help to normalize central obesity: (a) getting a negative energy balance by decreasing energy intake and/or increasing energy expenditure; (b) retarding or inhibiting nutrition absorption; (c) modulating metabolic responses; and (d) inducing microbiota abundance and composition [80].

Algae are composed among all of fiber matrix that contributes to the four just commented interventions, as fiber energy contribution is lower than nutrients contributing to decrease the meal energy content. In addition, fiber contributes to decrease nutrient digestion and absorption (overall fat and carbohydrates). Their gel capability formation increases satiety signals and slows down gastric emptying. This last effect contributing to lower TG and glucose postprandial responses, which induces a lower insulin secretion and improves insulin sensitivity helping to decrease IR, the atherogenic triad, the pro-oxidant, and inflammatory status [81]. Finally, fiber can be fermented by GM contributing to assure the instauration and colonization of low inflammatory and obesogenic microbiota that reduce colon and intestinal inflammatory and antioxidant status [80].

## 5.3. Gut Microbiota

The involvement of the microbiome in regulating carbohydrate and lipid metabolism has been discussed in the introduction. The prebiotic effect of algae is one mechanism underlying its antidiabetic properties [82]. There are many in vitro studies and in animal models focusing on the impact of whole algae or isolated component, mostly polysaccharides, consumption on the GM [83][82]. The defined composition of algae allows them to be classified as prebiotics. According to its definition, a prebiotic food serves as “a substrate that is selectively used by host microorganisms conferring a health benefit.” After this definition update, researchers paid attention to the same phytochemicals from seaweed not previously considered as prebiotic. Two interesting reviews have been published that delve into the prebiotic effect of seaweeds, with complete tables summarizing the major results [84][83]. An aspect of great relevance for understanding the complexity of the effects that occur at the colon level is that the influence between the microbiota and certain components of algae such as complex polysaccharides is bidirectional. The fermentation of these components can promote the growth of certain populations of beneficial bacteria, whereas others have been detrimental. Furthermore, how much these components will be fermented and, therefore, the production of bioavailable active metabolites from the algae, depends on the composition of the GM. This makes the prebiotic effects of algae depend on their composition (greatly variable) and on the microbiome of the patient/experimental animal that consumes it [85]. Relating to this question, it is worth highlighting a peculiarity of the fermentation of polysaccharides from algae, which does not affect terrestrial plants. The enzymes responsible for algae polysaccharide degradation (functional carbohydrate active enzymes, or shortly, CAZymes) are usually acquired by horizontal gene transfer, linked to regular consumption of algae. Due to the lack of specific enzymes, non-Asiatic people might not ferment algae when first times consuming them, losing their expected prebiotic effect [83]. Therefore, results about prebiotic properties of algae analyzed in vitro or in healthy animals must be carefully interpreted when discussing their implication relating to their antidiabetic effect. Thus, it is much more accurate to evaluate them in T2DM animal models, as dysbiosis may be presented, seaweed metabolism in this condition will be different, and their effect on microbiota could be changed. It cannot be generalized that prebiotic effects in healthy rodents will be kept in diabetic ones.

## 5.4. Antioxidant Properties



The T2DM multifactorial origin also shows oxidative stress a potential contributor toward this pathology development [86]; this is mainly due to two key factors, diet and the pathophysiology of T2DM itself. The inappropriate eating habits associated with this population, with diets rich in SFA and refined sugars, have proven to be an important source of free radicals and ROS. In addition, this pathology is normally associated with diabetic dyslipidemia and hyperglycemia alterations that induce ROS production and the subsequent redox state disbalance. Therefore, numerous nutritional strategies are aimed at reinforcing the antioxidant balance as a viable treatment against T2DM. As mentioned in the previous (Antioxidants: Polyphenols and Related Compounds), algae are an excellent source of antioxidant compounds. Any generalization on algal antioxidant compounds must be avoided, as algae composition depends on the species, habitat, and state of maturity, among other factors. Bocanegra et al. reviewed additional information on algae composition [10][87].

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