Algae and Type-2 Diabetes Mellitus

Subjects: Food Science & Technology

Submitted by: Aránzazu Bocanegra

Definition

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, ω-3 PUFAs, and bioactive molecules with potential antidiabetic activity.

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 [1]. 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 [2][3][4][5].

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 [6][7][8]. Algae contain a variety of nutrients and phytochemicals that exhibit various biological activities [9][10]. 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 [11][12]. 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 [13][14][15]. 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 [16][17]. 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 [18]. In fact, algae and their bioactive compounds are added as ingredients of functional foods (term coined for such foods with potential health benefits) [19][20]. 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 [20][21]. 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 [22][23]. 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 [24][25][26].

2. Type-2 Diabetes Mellitus

T2DM pathophysiology is due to a progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance (IR) by tissues such as skeletal muscle, liver, and adipose tissues (Figure 1) [27]. 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 [28].

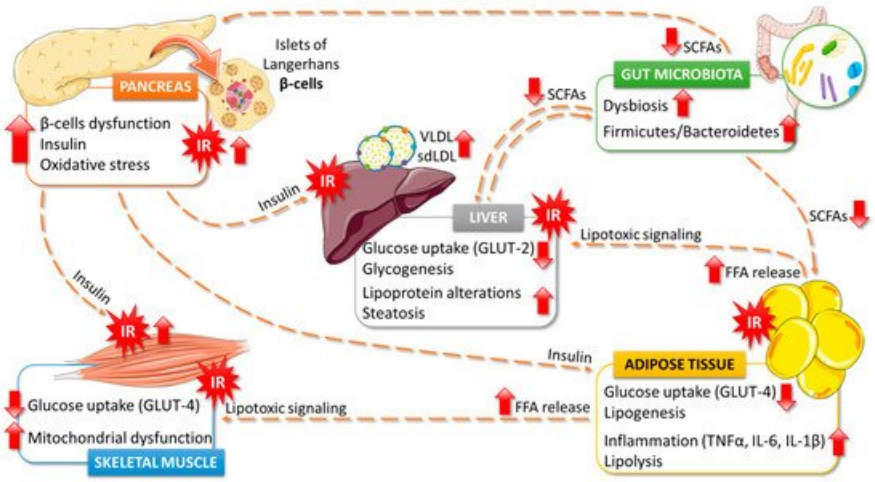

Figure 1. Representative scheme of the Type-2 diabetes mellitus pathophysiology. Main organs affected in T2DM and their interrelation in insulin resistance development. FFA, free fatty acids; GLUT-2, type 2 glucose transporter; GLUT-4, type 4 glucose transporter; IL-1β, interleukin 1 β; IL-6, interleukin 6; IR, insulin resistance; sdLDL, small dense low density lipoproteins; SCFAs, short-chain fatty acids; TNFα, tumor necrosis factor α; 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^{473} and Thr^{308}. 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 β-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 β-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-γ) [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
	Sargassum polycystum				
	Himanthalia elongata				

Division/Common Name	Specie	Pigments Chlorophyll a, c Fucoxanthins	Storage Product Laminarans	Cell Structural Wall Cellulose,	Intercellular Mucilage Alginic acid/Alginates,
Phaeophyta/Brown algae	*Undaria pinnatifida*	β-carotenes Xanthophylls	Mannitol	Chitin	Sulfated polysaccharides (Fucoidans)
	Laminaria spp.				
	Laminaria japónica, L digitata				
	Hizikia fusiforme				
Chlorophyta/Green algae	*Ulva spp*.	Chlorophyll a, b Xanthophylls	Starch	Cellulose, Xylans, Mannans	Sulfated polysaccharides
	Ulva lactuta				
	Ulva pertusa				
	Enteromorpha spp. (E. compresa)				
Rhodophyta/Red algae	*Pyropia spp.*	Phycoerythrin Phycocyanin Chlorophyll a	Florideans Starch	Cellulose, Xylans,	Sulfated polysaccharides (Agar,
	Pyropia tenera				
	Pyropia yezoensis				

Division/Common Name	Specie	Pigments	Storage Product	Cell Wall	Intercellular Mucilage
	Chondrus crispu	β-carotene Xanthophylls	Mannans	Structural	Carrageenans, Porphyrans)
	Gracilaria verrucosa				

* Adapted with permission from ref. [10]. Copyright 2021 Copyright MARY ANN LIEBERT, INC.

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) [47]. 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, β-carotene and several xanthophylls; green algae contain chlorophyll a and b and various characteristics xanthophylls [46][47].

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 [48].

3.2. Algal Consumption and Commercial Importance

Algae have been part of the human diet for thousands of years, based on archaeological evidence [49]. 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) [50]. The demand for edible seaweed is increasing in community markets and new production models and new market trends are emerging [50]; 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 [18][50]. For example, the direct consumption of brown algae as a human food dates back years and continues today as a valuable food ingredient [51][52].

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 [18][46]. 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 [18][46]. 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) [48][50]. Microalgae (Spirulina spp.) is also cultivated, although it is much under-reported. Australia, India, Israel, and Japan are among the producers of Spirulina [48].

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) [53]. 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*.) [49][53]. 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 [53]. 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 [53].

The composition of seaweeds is highly variable, depending not only on the species but also on the time of its collection and their habitat [53]. 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 [11][54]. 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 [11]. The biological activities reported for these components are varied [46][47]. 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 [55].

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 [56]. 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 [57]. 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 [43]. 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 [58].

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 [49]. 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.

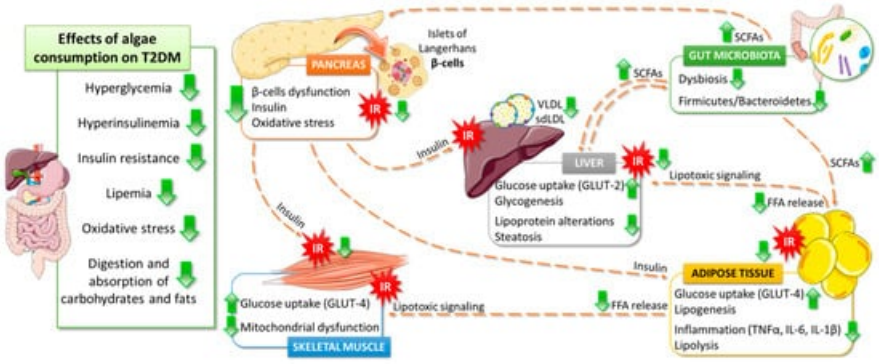

Figure 2. Effects of algae consumption on type 2 Diabetes Mellitus pathophysiology. Schematic representation of how algae consumption is able to modulate the different organs affected in T2DM. FFA, free fatty acids; GLUT-2, type-2 glucose transporter; GLUT-4, type 4 glucose transporter; IL-1β, interleukin 1 β; IL-6, interleukin 6; IR, insulin resistance; sdLDL, small dense low density lipoproteins; SCFAs, short-chain fatty acids; TNFα, tumor necrosis factor α; 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 alginate, 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. [71] 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 α-amylase and α-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].

References

1. World Health Organization. Global Report on Diabetes. 2016. Available online: (accessed on 10 January 2021).
2. Kolb, H.; Martin, S. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Med. 2017, 15, 1–11.
3. Laakso, M. Biomarkers for type 2 diabetes. Mol. Metab. 2019, 27, S139–S146.
4. Stančáková, A.; Laakso, M. Genetics of type 2 diabetes. Endocr. Dev. 2016, 31, 203–220.
5. Sharma, S.; Tripathi, P. Gut microbiome and type 2 diabetes: Where we are and where to go? J. Nutr. Biochem. 2019, 63, 101–108.
6. PR Newswire. Transparency Market Research. Available online: (accessed on 12 January 2021).
7. Koyande, A.K.; Chew, K.W.; Rambabu, K.; Tao, Y.; Chu, D.-T.; Show, P.-L. Microalgae: A potential alternative to health supplementation for humans. Food Sci. Hum. Wellness 2019, 8, 16–24.
8. Hannon, B.A.; Fairfield, W.D.; Adams, B.; Kyle, T.; Crow, M.; Thomas, D.M. Use and abuse of dietary supplements in persons with diabetes. Nutr. Diabetes 2020, 10, 14.
9. Jiménez-Escrig, A.; Goñi, I. Nutritional evaluation and physiological effects of edible seaweeds. Arch. Latinoam. Nutr. 1999, 49, 114–120.
10. Bocanegra, A.; Bastida, S.; Benedí, J.; Ródenas, S.; Sánchez-Muniz, F.J. Characteristics and nutritional and cardiovascular-health properties of seaweeds. J. Med. Food 2009, 12, 236–258.
11. Brown, E.M.; Allsopp, P.J.; Magee, P.J.; Gill, C.I.R.; Nitecki, S.; Strain, C.R.; McSorley, E.M. Seaweed and human health.

Nutr. Rev. 2014, 72, 205–216.
12. Xu, S.-Y.; Huang, X.; Cheong, K.-L. Recent advances in marine algae polysaccharides: Isolation, structure, and activities. Mar. Drugs 2017, 15, 388.
13. Peña-Romero, A.C.; Navas-Carrillo, D.; Marín, F.; Orenes-Piñero, E. The future of nutrition: Nutrigenomics and nutrigenetics in obesity and cardiovascular diseases. Crit. Rev. Food Sci. Nutr. 2018, 58, 3030–3041.
14. Mathers, J.C. Nutrigenomics in the modern era. Proc. Nutr. Soc. 2017, 76, 265–275.
15. Tiffon, C. The impact of nutrition and environmental epigenetics on human health and disease. Int. J. Mol. Sci. 2018, 19, 3425.
16. Amar, J.; Chabo, C.; Waget, A.; Klopp, P.; Vachoux, C.; Bermúdez-Humarán, L.G.; Smirnova, N.; Bergé, M.; Sulpice, T.; Lahtinen, S.; et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: Molecular mechanisms and probiotic treatment. EMBO Mol. Med. 2011, 3, 559–572.
17. Kolodziejczyk, A.A.; Zheng, D.; Shibolet, O.; Elinav, E. The role of the microbiome in NAFLD and NASH. EMBO Mol. Med. 2019, 11, e9302.
18. Barbier, M.; Charrier, B.; Araujo, R.; Holdt, S.L.; Jacquemin, B.; Rebours, C. PEGASUS—Phycomorph European Guidelines for a Sustainable Aquaculture of Seaweeds; Barbier, M., Charrier, B., Eds.; COST Action FA1406: Roscoff, France, 2019.
19. Holdt, S.L.; Kraan, S. Bioactive compounds in seaweed: Functional food applications and legislation. J. Appl. Phycol. 2011, 23, 543–597.
20. Macho-González, A.; Bastida, S.; Garcimartín, A.; López-Oliva, M.E.; González, P.; Benedí, J.; González-Muñoz, M.J.; Sánchez-Muniz, F.J. Functional meat products as oxidative stress modulators: A review. Adv. Nutr. 2021, nmaa182.
21. Mirmiran, P.; Bahadoran, Z.; Azizi, F. Functional foods-based diet as a novel dietary approach for management of type 2 diabetes and its complications: A review. World J. Diabetes 2014, 5, 267–281.
22. Schultz, A.R.; Garcimartín, A.; Bastida, S.; Jiménez-Escrig, A.; Rupérez, P.; Green, B.D.; Rafferty, E.; Sánchez-Muniz, F.J.; Benedí, J. Effects of Undaria pinnatifida, Himanthalia elongata and Porphyra umbilicalis extracts on in vitro α-glucosidase activity and glucose diffusion. Nutr. Hosp. 2014, 29, 1434–1446.
23. Garcimartín, A.; Benedi, J.; Bastida, S.; Sánchez-Muniz, F.J. Aqueous extracts and suspensions of restructured pork formulated with Undaria pinnatifida, Himanthalia elongata and Porphyra umbilicalis distinctly affect the in vitro α-glucosidase activity and glucose diffusion. LWT Food Sci. Technol. 2015, 64, 720–726.
24. Ródenas de la Rocha, S.; Sánchez-Muniz, F.; Gómez-Juaristi, M.; Larrea-Marín, M. Trace elements determination in edible seaweeds by an optimized and validated ICP-MS method. J. Food Compos. Anal. 2009, 22, 330–336.
25. Larrea-Marín, M.; Pomares-Alfonso, M.; Gómez-Juaristi, M.; Sánchez-Muniz, F.; de la Rocha, S.R. Validation of an ICP-OES method for macro and trace element determination in Laminaria and Porphyra seaweeds from four different countries. J. Food Compos. Anal. 2010, 23, 814–820.
26. Cherry, P.; O'Hara, C.; Magee, P.J.; McSorley, E.M.; Allsopp, P.J. Risks and benefits of consuming edible seaweeds. Nutr. Rev. 2019, 77, 307–329.
27. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013, 37, S81–S90.
28. Schlienger, J.-L. Complications du diabète de type 2. Presse Med. 2013, 42, 839–848.
29. Macho-González, A.; López-Oliva, M.E.; Merino, J.J.; García-Fernández, R.A.; Garcimartín, A.; Redondo-Castillejo, R.; Bastida, S.; Sánchez-Muniz, F.J.; Benedí, J. Carob fruit extract-enriched meat improves pancreatic beta-cell dysfunction, hepatic insulin signaling and lipogenesis in late-stage type 2 diabetes mellitus model. J. Nutr. Biochem. 2020, 84, 108461.
30. Beale, E.G. Insulin signaling and insulin resistance. J. Investig. Med. 2013, 61, 11–14.
31. Sánchez-Muniz, F.J.; García-Quismondo, A.; del Cañizo, F.J.; Dorado, J. Classical and emergent cardiovascular disease risk factors in type 2 diabetics from the Vallecas area (DICARIVA study). Nutr. Hosp. 2017, 34, 1432–1441.
32. Bays, H.E. "Sick Fat," metabolic disease, and atherosclerosis. Am. J. Med. 2009, 122, S26–S37.
33. Carmena, R. Dyslipemia in type 2 diabetes mellitus. In Type 2 Diabetes Mellitus; Serrano, M., Gutiérrez, J.A., Eds.; Elsevier España S.L.: Barcelona, Spain, 2010; pp. 219–230.
34. Chehade, J.M.; Gladysz, M.; Mooradian, A.D. Dyslipidemia in type 2 diabetes: Prevalence, pathophysiology, and management. Drugs 2013, 73, 327–339.
35. Athyros, V.G.; Doumas, M.; Imprialos, K.P.; Stavropoulos, K.; Georgianou, E.; Katsimardou, A.; Karagiannis, A. Diabetes and lipid metabolism. Hormones 2018, 17, 61–67.
36. Tangvarasittichai, S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes. 2015, 6, 456–480.
37. Qin, H.; Chen, Z.; Zhang, Y.; Wang, L.; Ouyang, P.; Cheng, L.; Zhang, Y. Triglyceride to high-density lipoprotein cholesterol ratio is associated with incident diabetes in men: A retrospective study of Chinese individuals. J. Diabetes Investig. 2020, 11, 192–198.
38. Chen, Z.; Hu, H.; Chen, M.; Luo, X.; Yao, W.; Liang, Q.; Yang, F.; Wang, X. Association of Triglyceride to high-density lipoprotein cholesterol ratio and incident of diabetes mellitus: A secondary retrospective analysis based on a Chinese cohort study. Lipids Health Dis. 2020, 19, 1–11.

39. Ojo, O. Dietary intake and type 2 diabetes. Nutrients 2019, 11, 2177.
40. Burgio, E.; Lopomo, A.; Migliore, L. Obesity and diabetes: From genetics to epigenetics. Mol. Biol. Rep. 2014, 42, 799–818.
41. Gesteiro, E.; Bastida, S.; Vázquez-Velasco, M.; Corella, D.; Guillén, M.; Ordovas, J.M.; Sánchez-Muniz, F.J. Effects of APOA5 S19W polymorphism on growth, insulin sensitivity and lipoproteins in normoweight neonates. Eur. J. Pediatr. 2011, 170, 1551–1558.
42. Gesteiro, E.; Sánchez-Muniz, F.J.; Ortega-Azorín, C.; Guillén, M.; Corella, D.; Bastida, S. Maternal and neonatal FTO rs9939609 polymorphism affect insulin sensitivity markers and lipoprotein profile at birth in appropriate-for-gestational-age term neonates. J. Physiol. Biochem. 2016, 72, 169–181.
43. Alkhatib, A.; Tsang, C.; Tiss, A.; Bahorun, T.; Arefanian, H.; Barake, R.; Khadir, A.; Tuomilehto, J. Functional Foods and Lifestyle Approaches for Diabetes Prevention and Management. Nutrients 2017, 9, 1310.
44. Wehr, J.D.; Sheath, R.G.; Kociolek, J.P. Freshwater Algae of North America. Ecology and Classification, 2nd ed.; Academia Press: San Diego, CA, USA; Elsevier: Oxford, UK, 2015; A volume in Aquatic Ecology; ISBN 9780123858771.
45. Ścieszka, S.; Klewicka, E. Algae in food: A general review. Crit. Rev. Food Sci. Nutr. 2019, 59, 3538–3547.
46. Tiwari, B.K.; Troy, D.J. Seaweed Sustainability. Food and Non-Food Applications, 1st ed.; Academic Press: Waltham, MA, USA; Elsevier: Oxford, UK, 2015; ISBN 978-0-12-418697-2.
47. Van den Hoek, C.; Mann, D.G.; Jahns, H.M. Algae: An Introduction to Phycology; Cambridge University Press: Cambridge, UK, 1995.
48. Ferdouse, F.; Løvstad-Holdt, S.; Smith, R.; Murúa, P.; Yang, Z. Food and Agriculture Organization of the United Nations. Available online: (accessed on 25 January 2021).
49. Wells, M.L.; Potin, P.; Craigie, J.S.; Raven, J.A.; Merchant, S.S.; Helliwell, K.E.; Smith, A.G.; Camire, M.E.; Brawley, S.H. Algae as nutritional and functional food sources: Revisiting our understanding. Appl. Phycol. 2017, 29, 949–982.
50. EUMOFA. Observatorio Europeo del Mercado de los Productos de la Pesca y de la Acuicultura. Available online: (accessed on 25 January 2021).
51. Tseng, C.K. Commercial cultivation. In The Biology of Seaweeds; Lobban, C.S., Wynne, M.J., Eds.; University of California Press: Berkeley, CA, USA; Blackwell Science Publications: Oxford, UK, 1981; Volume 17, pp. 680–725.
52. Afonso, N.C.; Catarino, M.D.; Silva, A.M.S.; Cardoso, S.M. Brown Macroalgae as Valuable Food Ingredients. Antioxidants 2019, 8, 365.
53. Food and Agriculture Organization of the United Nations (FAO). The State of World Fisheries and Aquaculture 2018—Meeting the Sustainable Development Goals; FAO: Rome, Italy, 2018; ISBN 978-92-5-130562-1.
54. Hafting, J.T.; Critchley, A.T.; Cornish, M.L.; Hubley, S.A.; Archibald, A.F. On-land cultivation of functional seaweed products for human usage. J. Appl. Phycol. 2012, 24, 385–392.
55. Stengel, D.B.; Connan, S.; Popper, Z.A. Algal chemodiversity and bioactivity: Sources of natural variability and implications for commercial application. Biotechnol. Adv. 2011, 29, 483–501.
56. Zheng, Y.; Ley, S.H.; Hu, F.B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. 2018, 14, 88–98.
57. Villanueva-Peñacarrillo, M.L.; Martín-Duce, A.; Ramos-Álvarez, I.; Gutiérrez-Rojas, I.; Moreno, P.; Nuche-Berenguer, B.; Acitores, A.; Sancho, V.; Valverde, I.; González, N. Characteristic of GLP-1 effects on glucose metabolism in human skeletal muscle from obese patients. Regul. Pept. 2011, 168, 39–44.
58. Cofrades, S.; Benedí, J.; Garcimartin, A.; Sánchez-Muniz, F.; Jimenez-Colmenero, F. A comprehensive approach to formulation of seaweed-enriched meat products: From technological development to assessment of healthy properties. Food Res. Int. 2017, 99, 1084–1094.
59. Shang, Q.; Song, G.; Zhang, M.; Shi, J.; Xu, C.; Hao, J.; Li, G.; Yu, G. Dietary fucoidan improves metabolic syndrome in association with increased Akkermansia population in the gut microbiota of high-fat diet-fed mice. J. Funct. Foods 2017, 28, 138–146.
60. Granado-Lorencio, F.; Hernández-Alvarez, E. Functional foods and health effects: A nutritional biochemistry perspective. Curr. Med. Chem. 2016, 23, 2929–2957.
61. Imamura, F.; Micha, R.; Wu, J.H.; de Oliveira Otto, M.C.; Otite, F.O.; Abioye, A.I.; Mozaffarian, D. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: A systematic review and meta-analysis of randomised controlled feeding trials. PLoS Med. 2016, 13, e1002087.
62. Shah, M.; Garg, A. The relationships between macronutrient and micronutrient intakes and type 2 diabetes mellitus in South Asians: A review. J. Diabetes Complicat. 2019, 33, 500–507.
63. Galbete, C.; Schwingshackl, L.; Schwedhelm, C.; Boeing, H.; Schulze, M.B. Evaluating Mediterranean diet and risk of chronic disease in cohort studies: An umbrella review of meta-analyses. Eur. J. Epidemiol. 2018, 33, 909–931.
64. The InterAct Consortium. Dietary fibre and incidence of type 2 diabetes in eight European countries: The EPIC-InterAct Study and a meta-analysis of prospective studies. Diabetologia 2015, 58, 1394–1408.
65. Malik, V.S.; Li, Y.; Tobias, D.K.; Pan, A.; Hu, F.B. Dietary Protein Intake and Risk of Type 2 Diabetes in US Men and Women. Am. J. Epidemiol. 2016, 183, 715–728.
66. Lee, K.W.; Woo, H.D.; Cho, M.J.; Park, J.K.; Kim, S.S. Identification of dietary patterns associated with incidence of

hyperglycemia in middle-aged and older Korean adults. Nutrients 2019, 11, 1801.
67. Lee, H.J.; Kim, H.C.; Vitek, L.; Nam, C.M. Algae consumption and risk of type 2 diabetes: Korean National Health and Nutrition Examination Survey in 2005. J. Nutr. Sci. Vitaminol. 2010, 56, 13–18.
68. Oba, S.; Nanri, A.; Kurotani, K.; Goto, A.; Kato, M.; Mizoue, T.; Noda, M.; Inoue, M.; Tsugane, S.; Japan Public Health Center-based Prospective Study Group. Dietary glycemic index, glycemic load and incidence of type 2 diabetes in Japanese men and women: The Japan public health center-based prospective study. Nutr. J. 2013, 12, 165.
69. Takahashi, K.; Kamada, C.; Yoshimura, H.; Okumura, R.; Iimuro, S.; Ohashi, Y.; Araki, A.; Umegaki, H.; Sakurai, T.; Yoshimura, Y.; et al. Effects of total and green vegetable intakes on glycated hemoglobin A1c and triglycerides in elderly patients with type 2 diabetes mellitus: The Japanese Elderly Intervention Trial. Geriatr. Gerontol. Int. 2012, 12, 50–58.
70. Paradis, M.-E.; Couture, P.; Lamarche, B. A randomised crossover placebo-controlled trial investigating the effect of brown seaweed (Ascophyllum nodosum and Fucus vesiculosus) on postchallenge plasma glucose and insulin levels in men and women. Appl. Physiol. Nutr. Metab. 2011, 36, 913–919.
71. Yoshinaga, K.; Mitamura, R. Effects of Undaria pinnatifida (Wakame) on postprandial glycemia and insulin levels in humans: A randomized crossover trial. Plant Foods Hum. Nutr. 2019, 74, 461–467.
72. Jensen, M.G.; Pedersen, C.; Kristensen, M.; Frost, G.; Astrup, A. Review: Efficacy of alginate supplementation in relation to appetite regulation and metabolic risk factors: Evidence from animal and human studies. Obes. Rev. 2013, 14, 129–144.
73. Tanemura, Y.; Yamanaka-Okumura, H.; Sakuma, M.; Nii, Y.; Taketani, Y.; Takeda, E. Effects of the intake of Undaria pinnatifida (Wakame) and its sporophylls (Mekabu) on postprandial glucose and insulin metabolism. J. Med Investig. 2014, 61, 291–297.
74. Kim, K.-T.; Rioux, L.-E.; Turgeon, S.L. Alpha-amylase and alpha-glucosidase inhibition is differentially modulated by fucoidan obtained from Fucus vesiculosus and Ascophyllum nodosum. Phytochemistry 2014, 98, 27–33.
75. Murray, M.; Dordevic, A.L.; Bonham, M.P.; Ryan, L. Do marine algal polyphenols have antidiabetic, antihyperlipidemic or anti-inflammatory effects in humans? A systematic review. Crit. Rev. Food Sci. Nutr. 2017, 58, 2039–2054.
76. Seung-Hong, L.; You-Jin, J. Anti-diabetic effects of brown algae derived phlorotannins, marine polyphenols through diverse mechanisms. Fitoterapia 2013, 86, 129–136.
77. Hall, A.; Fairclough, A.; Mahadevan, K.; Paxman, J. Ascophyllum nodosum enriched bread reduces subsequent energy intake with no effect on post-prandial glucose and cholesterol in healthy, overweight males. A pilot study. Appetite 2012, 58, 379–386.
78. Nesto, R.W. Beyond low-density lipoprotein: Addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am. J. Cardiovasc. Drugs 2005, 5, 379–387.
79. Ormazabal, V.; Nair, S.; Elfeky, O.; Aguayo, C.; Salomon, C.; Zuñiga, F.A. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc. Diabetol. 2018, 17, 122.
80. Sánchez-Muniz, F.J. IV y V Curso Avanzado en Obesidad y Síndrome Metabólico. Monografía 46; Instituto de España; Real Academia Nacional de Farmacia: Madrid, Spain, 2018.
81. Bocanegra, A.; Bastida, S.; Benedí, J.; Nus, M.; Sánchez-Montero, J.M.; Sánchez-Muniz, F.J. Effect of seaweed and cholesterol-enriched diets on postprandial lipoproteinaemia in rats. Br. J. Nutr. 2009, 102, 1728–1739.
82. Bermano, G.; Stoyanova, T.; Hennequart, F.; Wainwright, C.L. Seaweed-derived bioactives as potential energy regulators in obesity and type 2 diabetes. Adv. Pharmacol. 2020, 87, 205–256.
83. Cherry, P.; Yadav, S.; Strain, C.R.; Allsopp, P.J.; McSorley, E.M.; Ross, R.P.; Stanton, C. Prebiotics from seaweeds: An ocean of opportunity? Mar. Drugs 2019, 17, 327.
84. O'Sullivan, L.; Murphy, B.; McLoughlin, P.; Duggan, P.; Lawlor, P.G.; Hughes, H.; Gardiner, G.E. Prebiotics from marine macroalgae for human and animal health applications. Mar. Drugs 2010, 8, 2038–2064.
85. Lopez-Santamarina, A.; Miranda, J.M.; Mondragon, A.D.C.; Lamas, A.; Cardelle-Cobas, A.; Franco, C.M.; Cepeda, A. Potential use of marine seaweeds as prebiotics: A review. Molecules 2020, 25, 1004.
86. Faure, P. Protective effects of antioxidant micronutrients (vitamin E, Zinc and Selenium) in type 2 diabetes mellitus. Clin. Chem. Lab. Med. 2003, 41, 995–998.
87. Sánchez-Muniz, F.J.; Bocanegra, A.; Bastida, S.; Benedí, J. Algae and cardiovascular health. In Functional Ingredients from Algae for Foods and Nutraceuticals, 1st ed.; Domínguez, H., Ed.; Woodhead Publishing Limited: Cambridge, UK, 2013; pp. 369–415.

Keywords

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