Metabolic Disorders

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Contributor: Daniela Gabbia

Metabolic syndrome (MS) is a cluster of different metabolic disorders, obesity, hypertriglyceridemia, dyslipidemia, hyperglycemia, insulin resistance, and hypertension, that lead to an increased risk of developing type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular diseases (CVDs) [1]. In Western countries, the increased prevalence of CVDs and atherosclerosis, which actually accounted for approximately 50% of all CVD-related deaths, is further sustained by a sedentary lifestyle and high-calorie food intake [3]. It has been estimated that, in 2016, more than 1.9 billion adults (>18 of age) were overweight and 650 million were obese. A diet rich in fat and sugar and a lack of exercise leads to the accumulation of visceral fat, the development of liver steatosis, and the onset of MS risk factors. Since the prevalence of all these metabolic dysfunctions increased worldwide in the last years, it is essential to find new strategies for preventing or treating obesity, dyslipidemia, and insulin resistance [3], e.g. nutritional intervention and functional foods.

metabolic syndrome type 2 diabetes nutritional intervention

1. Introduction

Metabolic syndrome (MS) is a cluster of different metabolic disorders, which lead to an increased risk of developing type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular diseases (CVDs), thereby reducing patients' quality of life and increasing morbidity and mortality [1]. As far as CVDs are concerned, according to the World Health Organization (WHO), CVD-related mortality is rapidly increasing in the world, since 17.5 million deaths occurred in 2012, and these are estimated to reach 22.2 million in 2030 [2]. Since the prevalence of all these metabolic dysfunctions increased worldwide in the last years, it is essential to find new strategies for preventing or treating obesity, dyslipidemia, and insulin resistance [3], which are all well-recognized risk factors for MS.

The first-line therapy for MS involves drugs treating MS comorbidities and their symptoms. Although these drugs can be helpful, many of them lead to serious side-effects, and their efficacy could be reduced or lost with chronic administration. Thus, nutritional interventions have been proposed to reduce the risk of MS by preventing and alleviating chronic dietary-associated disorders [4][5].

In the last few decades, it has been demonstrated that a number of natural compounds exert multiple beneficial effects, such as anti-inflammatory, anti-hyperglycemic, and lipid-lowering activities, ameliorating blood lipid and glucose levels and insulin sensitivity [3][6][7]. Among these natural products, growing interest has been given to seaweeds, by virtue of their micro- and macronutrient content. They have been and are currently used in nutraceuticals and functional foods for the management of MS comorbidities [8]. Further supporting the effectiveness of seaweeds in treating and preventing MS, much epidemiological evidence has demonstrated that a lower incidence of obesity and diet-related disease is reported in countries where seaweeds are regularly consumed within the diet (for example, Japan) with respect to Western countries [9][10][11].

Seaweeds display peculiar chemical properties compared to terrestrial plants by virtue of their mineral-rich marine habitat, which requires specific adaptative responses for their survival. Thus,

seaweeds are able to generate many bioactive metabolites with antioxidant and antimicrobial properties to counteract the abiotic stress typical of the marine environment—e.g., UV photo-damage, high salinity, constant oxygen exposure, and biotic stress induced by bacterial colonization and marine herbivores [8]. Interestingly, these bioactive compounds can be easily extracted and purified by novel eco-friendly techniques [12][13][14].

Seaweeds were classified into three main classes or phyla: brown seaweeds (Ochrophyta), red seaweeds (Rhodophyta), and green seaweeds (Chlorophyta). Each phylum comprises thousands of algal species, many of which have been used since old times as food, folk remedies, dyes, and fertilizers [8][15][16]. Among the traditional dishes of East Asian countries (Korea, China, and Japan), many brown seaweeds are used—for example, in Wakame (Undaria), Konbu (Laminaria), Nori/Gim, and Hijiki (Hizikia). They represent a high-quality and healthy ingredient for food preparation by virtue of their low content of lipids and high content of polysaccharides, fibers, and polyunsaturated fatty acids (PUFAs). Moreover, they are rich in vitamins; minerals; and bioactive secondary metabolites—e.g., polyphenols, fucoidans, pigments, mycosporine-like amino acids (MAAs), and terpenoids [17][18].

2. Clinical Studies Investigating Brown Seaweeds for MS Treatment

Many studies investigating the activity of brown seaweeds are performed by in vitro or in vivo evaluations on cell lines or animal models, respectively, providing valuable information regarding the identification of the bioactive components responsible for the effect and the signaling pathways involved. For example, a number of in vivo animal studies have demonstrated the anti-diabetic and hypoglycemic efficacy of brown seaweeds [4][19][20][21][22]. The principal mechanism involved in this activity is the inhibition of digestive enzymes (e.g., α-amylase, α-glucosidase, lipase, PTP1B), which causes a reduction in dietary fat and glucose absorption, and the hepatic gluconeogenesis. These effects are mainly due to algal phlorotannins, fucoxanthin, polyphenols, and polysaccharides [23][24]. Nevertheless, clinical studies are a fundamental step for the evaluation of the effective and safe use of algal extracts and are necessary to identify the molecular identity of effective compounds. E. cava, U. pinnatifida, A. nodosum, and F. vesiculosus are the most investigated brown seaweeds for the management of MS-related disease. Table 1 describes the principal clinical studies dealing with the efficacy of brown algae in MS comorbidities.

Table 1. Principal clinical studies investigating the effect of brown seaweeds in MS comorbidities.

Brown Seaweeds	Bioactive Compound	Study Design and Population	Observed Effect	Refs.
A. nodosum and F. vesiculosus	**Polyphenols, fibers, minerals**	**Double-blind, placebo-controlled, cross-over randomized trial with 23 men and women (18–60 years) with BMI 20–30 Kg/m^2.**	**Decrease in insulin iAUC. Increase in the Cederholm index of insulin sensitivity.**	**[25]**
A. nodosum and F. vesiculosus	**Phlorotannins**	**60 men and women (18–65 years).**	**Improvement of postprandial cognitive performance and drowsiness.**	

Brown Seaweeds	Bioactive Compound	Study Design and Population	Observed Effect	Refs.
A. nodosum and F. vesiculosus	Polyphenol extract (titrated to 20%)	65 dysglycemic patients.	Reduction in HbA1c, fasting plasma glucose, postprandial plasma glucose, fasting plasma insulin, high sensitivity C-reactive protein, and HOMA-IR. Improve insulin sensitivity and glycemic status.	[26]
A. nodosum and F. vesiculosus	Polyphenol extract (titrated to 20%)	50 men and women (18–60 years), 44 overweight and 6 obese.	Reduction in waist circumference, plasma glucose, and insulin and HOMA index.	[27]
A. nodosum	Polyphenols (phlorotannins)	Double-blind, randomized, placebo-controlled crossover trial with 80 subjects (30–65 years) with BMI ≥ 25 Kg/m^2.	Decrease in DNA damage in obese subjects. No significant changes in CRP, inflammatory cytokines, and antioxidant status.	[28]
F. vesiculosus	Polyphenols	Double-blind, placebo-controlled, randomized, cross-over trial with 38 volunteers (26 non-Asian, 12 Asian, 19–56 years).	No lowering effect on postprandial glucose or insulin responses in healthy subjects. Different insulin sensitivity in Asian subjects.	[29]
E. cava	Dieckol	Double-blind, placebo-controlled, randomized trial with 80 men and women (20–65 years) with a fasting glucose between 100 and 180 mg/dL.	Decrease in postprandial glucose, insulin, and C-peptide levels.	[30]
E. cava	Polyphenols. Including dieckol, 8,8’-bieckol, 6,6’-bieckol, and phlorofurofucoeckol A	Double-blind, placebo-controlled, randomized trial with 97 men and women (19–55 years) with BMI 24–29 Kg/m^2.	Decrease in BMI, body fat ratio, waist circumference, waist/hip ratio, total cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol/high-density lipoprotein (HDL), cholesterol, and atherogenic index. High dosage showed also significant decreases in serum glucose and systolic blood pressure.	[31]
E. cava	Polyphenols (dieckol)	Double-blind, placebo-controlled, randomized trial with 80 healthy subjects (19–80 years) with total cholesterol > 200 mg/dL or of LDL cholesterol > 110 mg/dL.	Decrease in total cholesterol and LDL cholesterol levels.	[32]

Brown Seaweeds	Bioactive Compound	Study Design and Population	Observed Effect	Refs.
U. pinnatifida and L. japonica	Indigestible polysaccharides dietary fiber	20 T2D patients (men and women, 40–70 years).	Improvement of blood glucose levels, serum TG decrease. Increase in HDL cholesterol and activity of CAT and glutathione peroxidase.	[33]
U. pinnatifida	Fresh Wakame or Mekabu	Randomized, crossover study with 12 healthy adults (men and women).	Reduction in plasma glucose levels, due to the improvement of glycemic index of foods.	[34]
U. pinnatifida	Dried Wakame powder	36 elderly outpatients with hypertension.	Decrease in systolic and diastolic blood pressure. Improvement of hypercholesterolemia.	[35]
U. pinnatifida	Dried algal powder	27 patients (men and women) with at least one symptom of MS.	Decrease in systolic blood pressure and waist circumference.	[36]
U. pinnatifida	Fucoxanthin	Double-blind, randomized, placebo-controlled study of 115 obese, premenopausal, non-diabetic women with and without NAFLD.	Decrease in body weight, waist circumference, body and liver fat content. Improvement in liver function tests and resting energy expenditure.	[37]
Kelp Laminaria	Fucoxanthin	Randomized, double-blind, placebo-controlled crossover trial with 50 men and women (20–59 years) with a BMI of > 26–30 Kg/m2 and waist circumference of ≥90 cm (women) and ≥85 cm (men).	Decrease in body weight, BMI, and visceral fat.	[38]
L. japonica	Fucoidan	Double-blind, placebo-controlled, randomized trial with 25 overweight or obese adults (30–60 years).	Decrease in diastolic blood pressure and LDL-C. Increase in insulin levels, HOMA β-cell, and HOMA IR.	[39]
Fermented L. japonica	5.56%-aminobutyric acid (GABA)	Randomized, controlled trial with healthy subjects with high levels of γ-GT (< 132 U/L).	Decrease in serum γ-GT and malondialdehyde. Reduction in oxidative stress. Increases antioxidant activity of CAT and SOD.	[40]
S. horneri	Fucoxanthin	Single-blinded and randomized study with 60 normal-weight and obese Japanese adults with a BMI > 22 Kg/m^2.	Decrease in HbA1c levels.	[41]

3. Conclusions and Future Trends

Brown seaweeds represent a sustainable and low-cost source of a variety of bioactive compounds,

displaying multiple beneficial effects for human health. Being a low-caloric food free of saturated fat, they could represent an excellent alternative for the intake of n-3 FAs derived from fish and are suitable for many functional food applications. For these reasons, there is a growing interest in their use for medicinal applications, mainly for lifestyle-related diseases such as T2DM, hypertension, obesity, and cardiovascular diseases, all of which are associated to MS development. To support this evidence, the global seaweed market is evaluated to rise from $10.4 billion as of 2015 to $14.7 billion as of 2021 [8].

As extensively described above, the mechanisms by which bioactive algal components could exert their effect have been investigated using many cell lines and animal models—e.g., adipocytes, high fat-fed rats or mice, and genetically modified mice [4][42][19][20][43]. Furthermore, a number of controlled clinical trials conducted in men and women adults and older have demonstrated in the last few years the potential of the use of brown seaweeds for the management of MS comorbidities (Table 1), further confirming the results obtained by in vitro and in vivo studies.

MS comorbidities were traditionally considered as diseases of adulthood; nevertheless, the increasing incidence of obesity between children and adolescents has raised the need for safe and effective agents to be used at different ages to prevent obesity. Furthermore, juvenile obesity could predispose one to T2DM, hypertension, dyslipidemia, NASH, left ventricular hypertrophy, obstructive sleep apnea, psychosocial complications, and orthopedic problems in adult life [1][42][44]. Interestingly, a Japanese interventional study investigated the effect of the red seaweed nori on blood pressure in children aged 4 to 5 years, observing a decrease in diastolic blood pressure in boys [45]. The authors thus suggest that nori seaweed might represent a preventive intervention for treating elevated blood pressure in childhood. This study represents the first attempt to use seaweeds in young people as a supplement for MS comorbidities, and could open a new perspective also for the future development of brown seaweed use.

Furthermore, seaweeds have been used for enhancing the antioxidant activity of gluten-free baked products, and this application opens new avenues in the enrichments of foods dedicated to coeliac patients [46].

In conclusion, brown seaweeds have demonstrated a great potential as food supplements for MS management. However, some issues still need to be deepened to improve the knowledge of their ADME in humans, find validated indexes of algal absorption, and obtain reliable information on their efficacy and long-term safety.

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