Effects of Microalgae on Metabolic Syndrome

Subjects: Medicine, Research & Experimental

Contributor: Kartthigeen Tamel Selvan , Jo Aan Goon , Suzana Makpol , Jen Kit Tan

Metabolic syndrome (MetS) is a cluster of metabolic disturbances, including abdominal obesity, hypertension, hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C) and hyperglycemia. Adopting a healthier lifestyle and multiple drug-based therapies are current ways to manage MetS, but they have limited efficacy, albeit the prevalence of MetS is rising. Microalgae is a part of the human diet and has also been consumed as a health supplement to improve insulin sensitivity, inflammation, and several components of MetS.

microalgae | metabolic syndrome | obesity | hypertension | hypertriglyceridemia | high-density lipoprotein cholesterol | hyperglycemia | type 2 diabetes mellitus | cardiovascular disease

1. Introduction

Metabolic syndrome (MetS) is a cluster of metabolic disturbances including abdominal obesity (elevated waist circumference), hypertension, hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C) and hyperglycemia, which are some of the major risk factors for developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [1]. For MetS to be clinically diagnosed, one must have at least three of those metabolic disturbances [1][2][3][4][5]. The occurrence of non-alcoholic fatty liver disease (NAFLD), which is defined by an excessive hepatic accumulation of triglycerides and cholesterol gallstone disease, are two main manifestations of MetS in the liver [1][6]. Moreover, insulin resistance (IR) is one of the crucial factors involved in the etiology of MetS and its comorbidities due to the important role of insulin in regulating energy, glucose, and lipid metabolism [1][7][8]. Therefore, IR is also involved in the pathogenesis of NAFLD, T2DM, obesity and CVD [9]. These conditions are connected by low-grade inflammation, which is a key pathophysiological process in the pathogenesis and growth of disturbances associated with MetS [10]. In that context, the release of pro-inflammatory cytokines and adipokines by immune cells and adipose tissues mediate the state of inflammation in the body leading to IR, exacerbation of NAFLD and development of CVD [9][10].

Microalgae are unicellular and photosynthetic microscopic algae that live in fresh or saltwater which comprise eukaryotic microalgae and prokaryotic cyanobacteria [11][12]. From the human consumption perspective, microalgae are cultivated commercially for application in the food and cosmetic industries. Microalgae biomass and their extracts, such as pigments, carotenoids, fatty acids and proteins, have been incorporated as additives or ingredients in food products such as biscuits, bread, cookies, snacks, milk, yogurt, and pasta [13][14][15][16]. Microalgae are emerging sources of bioactive components such as polysaccharides (especially β-1,3-glucan),

carotenoids, pigments and water extracts in cosmetic products namely lotions, creams, shampoos, and soaps that are marketed with anti-aging, UV protective and moisturizing properties [16][17][18][19]. Eukaryotic microalgae such as *Chlorella* sp., *Dunaliella salina*, *Haematococcus pluvalis*, *Crypthecodinium cohnii* and *Shizochytrium*, and prokaryotic cyanobacteria such as *Arthrospira plantesis* and *Aphanizomenon flos-aquae* are the most popular microalgae species used for human consumption but many other species are yet to be explored [16][20][21].

2. In Vitro Study

A cell model representing MetS is yet to be reported in the literature, probably because some MetS criteria are improbable to be measured in a cell-based study. Interestingly, a study has assessed the microalgae-derived products in several cell models that closely recapitulate some MetS criteria in a well-designed study that compared with the positive control drugs (**Table 1**).

Table 1. The effects of microalgae supplementation on MetS-related cell model.

Experiment	Cell Model	Microalgae and Doses	Experimental Groups	Effects	Mechanisms	Reference Number
Dose-response analysis	COS-1 cells	0.1% *Chaetoceros karianus*-derived (7E)-9-OHE or (10E)-9-OHE for 18 h	(1) Positive controls: rosiglitazone or pirinixic acid (2) (7E)-9-OHE or (10E)-9-OHE (3) Negative control: palmitic acid	(7E)-9-OHE or (10E)-9-OHE: Exhibits PPARα/γ agonist activity	-	[22]
Endogenous PPAR target genes activation analysis	Huh7 cells SGBS pre-adipocyte cells	• 25 or 50 µM (7E)-9-OHE or (10E)-9-OHE for 24 h • 2 µM rosiglitazone for 24 h	(1) DMSO (negative controls) (2) 25 µM (7E)-9-OHE or (10E)-9-OHE (3) 50 µM (7E)-9-OHE or (10E)-9-OHE (4) pirinxic acid (positive control)	25 or 50 µM of (7E)-9-OHE or (10E)-9-OHE: Fatty acid catabolism is activated in Huh-7 and SGBS cells	Huh-7: (7E)-9-OHE: ↑ ACSL3 gene expression (10E)-9-OHE: ↑ PLIN1 gene expression (7E)-9-OHE or (10E)-9-OHE: ↑ CPT1A and	

Experiment	Cell Model	Microalgae and Doses	Experimental Groups	Effects	Mechanisms	Reference Number
					ANGPTL4 gene expressions SGBS: (10E)-9-OHE: ↑ ANGPTL4 gene expression (7E)-9-OHE or (10E)-9-OHE: ↑ CPT1A gene expression	
Adipocyte differentiation analysis	SGBS pre-adipocyte cells	25 µM of (7E)-9-OHE or (10E)-9-OHE for 12 days	(1) (7E)-9-OHE or (10E)-9-OHE (2) rosiglitazone (positive control)	Improvement in the regulation of fatty acid metabolism, transport, storage, adipokine signaling and browning	↑ PPARG, CEBPA, CEBPB, PLIN1, FABP4, CD36, SCD1 and UCP1 expressions	
Adipocyte transcriptomics	SGBS pre-adipocyte cells	25 µM of (7E)-9-OHE or (10E)-9-OHE for 8 days	(1) (7E)-9-OHE or (10E)-9-OHE (2) rosiglitazone (positive control)	↓ Inflammatory cytokines ↑ Insulin-sensitive adipokines	↓ IL-6, TNFα, CXCL1, CXCL5 and IL-1B gene expressions ↑ Leptin and insulin sensitizing ADIPOQ genes expressions	

are types of nuclear receptors found in the human liver and adipose tissue, respectively. These are ligand-activated receptors that heterodimerize with retinoid X receptors (RXRs) to regulate gene expression by acting as transcriptional factors [22]. Activated PPARγ modulates the growth and differentiation of adipocytes through the upregulation of lipogenesis and lipid storage genes, and functions to regulate insulin sensitivity by promoting the synthesis of adiponectin and leptin and improvement of hyperglycemia [23][24][25][26]. In contrast, activated PPARα is involved in the uptake, activation, and oxidation of fatty acids in the liver [25]. Impairment in these PPARs is related to obesity, IR, and diabetes mellitus, which are some of the conditions associated with MetS [24]. PPAR agonists such as thiazolidinedione (targets PPARγ) and fibrates (targets PPARα) have been proven to improve insulin sensitivity and hyperlipidemia, respectively [23][24][25][26].

ACSL5: acyl-CoA synthetase long-chain family members 5, ADIPOQ: adipokine adiponectin, CD36: cluster of differentiation 36, CEBPA: CCAAT enhancer-binding protein alpha, CEBPB: CCAAT enhancer-binding protein beta, CPT1A: carnitine palmitoyltransferase 1A, CXCL1: CXC motif chemokine ligand 1, CXCL5: CXC motif chemokine ligand 5, FABP4: fatty acid binding protein 4, IL-1B: interleukin-1 beta, IL-6: interleukin-6, OHE: oxohexadecenoic acid, PLIN1: perilipin 1, PPARα: peroxisome proliferator activated receptor, PPARG: peroxisome proliferator activated receptor gamma, SCD1: Stearoyl-CoA desaturase 1, SGBS: Simpson–Golabi–Behmel syndrome, TNFα: tumor necrosis factor α, UCP1: uncoupling protein 1.

Long-chain fatty acids such as oxo-fatty acids (oFAs) are involved in different physiological processes that appear to be connected to the pathophysiological state caused by obesity such as IR, diabetes, and cardiovascular diseases [27][28][29]. A study has found that oFAs produced by gut bacteria exhibited PPARγ ligand activity which may be used to modulate the host's energy metabolism [29]. In line with this, (7E)-9-oxohexadec-7-enoic acid [(7E)-9-OHE] and (10E)-9-oxohexadec-10-enoic acid [(10E)-9-OHE], which are two novel oxo-fatty acids identified from the microalgae *C. karianus*, have been reported to exhibit considerable PPARα/γ agonist activity [25]. Another study found that OFAs produced by gut bacteria have previously been shown to promote the secretion of cholecystokinin (CCK) to improve postprandial glycemia, lipidemia, and appetite but its PPAR agonist activity was not assessed [30].

Sæther et al. investigated the potential of oFAs, [(7E)-9-OHE] and [(10E)-9-OHE] from *C. karianus* in activating PPAR in hepatocytes and adipocytes [22]. Preliminarily, the dose-dependent effects of both oFAs were studied in COS1 cells (a fibroblast-like cell line derived from African green monkey kidney) treated with (7E)-9-OHE, (10E)-9-OHE, pirinixic acid, rosiglitazone, or palmitic acid for 18 h. The results show that both oFAs produce considerable dose-dependent PPAR agonist activity. In that context, both oFAs demonstrated similar potency as pirinxic acid, which is a positive control, in activating the PPARα receptor. As for PPARγ activation, the oFAs had lower potency and efficacy compared to rosiglitazone which is another positive control but the PPRAγ activation was still higher compared to palmitic acid being the negative control. To determine the endogenous PPAR target genes activated by the oFAs in the liver, Huh-7 was treated with (7E)-9-OHE or (10E)-9-OHE. The results showed that the oFAs treatment was able to activate fatty acid catabolism in hepatocytes. In that context, the oFAs upregulated the expressions of CPT1A and ANGPTL4 due to the activation of the PPARα receptor. Moreover, ACSL3 and PLIN1 genes were significantly upregulated by treating the cells with (7E)-9-OHE and (10E)-9-OHE, respectively. CPT1A gene functions to synthesize the CPT1 enzyme, which is the rate-limiting enzyme for fatty acid β-oxidation, and the ACSL3 gene encodes for acyl-CoA synthetases that convert FAs into fatty acyl-CoA esters which participate in β-oxidation [31][32]. Besides that, the ANGPTL4 gene functions to modulate TG and energy homeostasis according to body state [32][33][34]. ANGPTL4 expression has been shown to improve glucose tolerance and hyperglycemia in diabetic mice which suggests that it can improve glucose metabolism [35]. Lastly, PLIN1 is involved in modulating lipolysis depending on energy requirement, so these genes also regulate lipid metabolism in the liver [36]. The endogenous PPAR target genes activation by the oFAs was also determined in SGBS adipocytes. The SGBS cells were originally pre-adipocytes that were differentiated in an adipogenic medium for 8 days. At day 8, the SGBS cells were stimulated with (7E)-9-OHE, (10E)-9-OHE or rosiglitazone medium for 24 h. The results show that both oFAs induce fatty acid catabolism in adipocytes by upregulating CPT1A expression. In adipose tissue, CPT1A improves fatty acid-induced IR and reduces TG accumulation [31]. Moreover, in SGBS cells treated with (10E)-9-OHE, ANGPTL4 expression was upregulated. Apart from its effect on TG metabolism, ANGPTL4 also functions as an adipokine in inducing adipocyte differentiation and adipose tissue expansion [33]. Overall, the findings suggest that oFAs play a role in regulating adipocyte metabolism but are not as efficacious as the drug, rosiglitazone.

Next, the study compared the adipogenic potentials of the oFAs with rosiglitazone. Here, the SGBS cells were differentiated in a medium containing (7E)-9-OHE, (10E)-9-OHE or rosiglitazone for 12 days in which the medium was renewed every 4 days. The results show that both oFAs increased the number of adipocyte-like cells and total

volume of lipid droplets upon Oil-Red-O staining but not as profound as rosiglitazone-treated cells. The author stated that the RNA analysis suggests that the oFAs were able to promote the regulation of fatty acid metabolism, transport, storage, adipokine signaling and browning. In that context, the oFAs upregulated PPARG, CEBPA, CEBPB, PLIN1, FABP4, CD36 and SCD1 gene expressions. CEBPB promotes the expression of PPARG and CEBPA, being the key event in adipocyte differentiation [37]. Meanwhile, the FABP4 gene functions to maintain adipocyte homeostasis [38], while the CD36 gene may play a role in modulating adipocyte hyperplasia and hypertrophy [39]. SCD1 gene produces the rate-limiting enzyme in the synthesis of MUFAs involved in lipogenesis [40]. So, the upregulation of these genes favors adipogenesis. However, these gene expressions were 5 to 10-fold higher with rosiglitazone. The author suggested that with oFAs treatment, only temporary upregulation of crucial adipogenic genes such as PPARG and C/EBPa genes was possible but a more stable expression is exhibited when treated with rosiglitazone. Furthermore, the oFAs upregulate UCP1 gene expression, although not as profoundly as rosiglitazone. The UCP1 gene is crucial in the event of adipose tissue (AT) browning [37]. Adipose tissue can be divided into white and brown. White adipose tissues (WAT) function to store excess energy as TG and release adipokines that are involved in the regulation of energy metabolism. Moreover, brown adipose tissue (BAT) functions as a thermogenic organ and protects against obesity and certain metabolic disturbances. Therefore, adipose tissue dysfunction and/or imbalance in their composition can lead to metabolic derangements [41][42]. Hence, these oFAs have the potential to induce adipose tissue browning that is associated with improvement in dyslipidemia and obesity.

To further reveal the difference between the oFAs and rosiglitazone in stimulating adipocyte differentiation, adipocyte transcriptomic analyses were included in this work. As a result, it was shown that the adipogenic effects of the oFAs were considerable but still lower compared to rosiglitazone. This may not appear ideal since fatty acid uptake and adipogenesis are important effects exerted by PPARγ agonists in the attempt to alleviate dyslipidemia. However, considering the side effects of thiazolidinediones (rosiglitazone) such as weight gain and edema [24], oFAs are still potential substitutes. Furthermore, the oFAs were able to upregulate the expressions of leptin and the insulin-sensitizing adipokine adiponectin (ADIPOQ) genes. Moreover, PPARγ activation by the oFAs is associated with the suppression of pro-inflammatory cytokines gene expressions such as IL-6, TNFa, CXCL1, CXCL5 and IL-1B. Additionally, the expression of IRS1 and SLC2A4 genes was increased. Increased expression of IL-1B is linked to the downregulation of IRS1 and SLC2A4 genes which leads to reduced adipose insulin sensitivity. Therefore, these oFAs are termed as semi-potent dual PPARα/γ agonists and activate anti-diabetic gene programs via suppressing pro-inflammatory cytokines and increasing insulin-sensitive adipokines. As such, dual PPARα/γ agonists activity of the oFAs has the potential to alleviate hyperglycemia and dyslipidemia which are crucial components of MetS.

3. In Vivo Studies

Many studies have reported the effects of microalgae on the individual components of MetS using obese, diabetic and hypertension animal models. However, these models might not be the best to represent MetS because the status of other components was not evaluated or might not be affected by the component-specific models. Hence,

the actual therapeutic potential of microalgae on MetS is difficult to appreciate. Therefore, this section will only include those studies that have established the MetS models by measuring most if not all the parameters that are sufficient to define the presence of MetS and discuss the effects of microalgae on these components (**Table 2**).

Table 2. The effects of microalgae supplementation on MetS-induced animal models.

Animal Model	Microalgae and Doses	Experimental Design	Effects on MetS	Mechanisms	Reference Number
Male Sprague Dawley rat (7 weeks old)	*Tetraselmis chuii* powder (0.17, 1.7, 17 mg/kg BW/d) 8 weeks	STD-C: Standard diet-control CAF-C: Cafeteria diet-control CAF + 0.17: CAF + 0.17 mg/kg BW/day of *T. chuii* powder CAF + 1.7: CAF + 1.7 mg/kg BW/day of *T. chuii* powder CAF + 17: CAF + 17 mg/kg BW/day of *T. chuii* powder	CAF + 0.17: ↓ plasma LDL/VLDL-C CAF + 17: ↓ Plasma glucose CAF + 0.17, CAF + 1.7 and CAF + 17: No effects on BW, adiposity index, TG, HOMA-IR index, and HDL-C.	CAF + 0.17: ↑ plasma NOx ↑ GPx activity in liver CAF + 0.17 and CAF + 1.7: ↑ SOD 1 and SOD2 gene expression in liverCAF + 1.7 and CAF + 17: ↑ GPX1 gene expression in liver ↑ GCLm gene expression in liver CAF + 17: ↓ oxLDL levels in plasma ↑ IL-10 levels in plasma ↑ GSH level in liver ↑ SOD1 gene expression in liver ↑ IL-10 gene expression in MWAT ↑ FOXP3 gene expression in spleen CAF + 0.17, CAF + 1.7 and CAF + 17: ↑ GR and GSH-S gene expressions in liver ↑ SOD1 gene expression in liver ↓HMOX1, TGFβ1 and NFκB1 gene expressions in liver ↓ IL-1β, TNFα and	[43]

Animal Model	Microalgae and Doses	Experimental Design	Effects on MetS	Mechanisms	Reference Number
				IFNG gene expressions in MWAT ↓ IL-1β agene in thymus and spleen ↓ IFNG gene expressions in MWAT, thymus and spleen ↑ ACDC gene expression in MWAT ↓ TNFα, NRF2, HMOX1, NFκB1, IL-1β and IFNG gene expressions in thymus ↑ IL-10 gene expression in thymus and spleen	
Female Sus scrofa pigs(5.6 ± 0.8 months old)	*Arthrospira platensis* (spirulina, Sp) (20 g/d) tablet 25 weeks	CTR−: Control diet CTR+: Control diet + Sp tablet WES−: Western diet WES+: Western diet + Sp tablet	CTR+ and WES+: No effects on BW No effects on visceral adipose tissue proportion No effects on plasma TG No effects on plasma TC ↓ Serum glucose (at late gestation)	CTR+: ↓ ALT levels ↓ Hepatic necrosis gene expression WES+: ↑ Hepatic lipid accumulation gene expression ↓ Hepatic carbohydrate accumulation gene expression ↑ ALT levels ↑ Hepatic necrosis gene expression CTR+ and WES+: ↓ Plasma insulin levels (at slaughter) ↓ Muscular weight gain gene expression ↓ Liver weight ↓ IR gene expression in liver	[44]
Male Wistar rat	*Diacronema lutheri* powder (12%)	CTRL: Control diet	HF-Dia: ↓ BW	HF-Dia: ↓ Plasma insulin	[45]

Animal Model	Microalgae and Doses	Experimental Design	Effects on MetS	Mechanisms	Reference Number
(3 weeks old)	8 weeks	HF: High fat diet HF-Dia: High fat + *D. lutheri* powder	↓ AAT and EAT weight/BW ratio ↓ Plasma TG levels ↑ HDL levels ↓ HOMA-IR index Improvement in GT & IT No effects on plasma glucose levels	levels ↓ AIP ↑ Plasma IL-4 levels ↑ Adipose IL-10 levels ↓ Leptin ↓ TG in liver ↓ TC in liver ↑ ALT ratio	
Male Wistar rat (8–9 weeks old)	*Nannochloropsis oceanica* powder (5%) 8 weeks	C: Corn starch diet for 16 weeks H: High-carbohydrate, high-fat diet for 16 weeks CN: Corn starch diet for the first 8 weeks + 5% *N. oceanica* powder for the last 8 weeksHN: High-carbohydrate, high-fat diet for first the 8 weeks + 5% *N. oceanica* powder for the last 8 weeks	HN: ↓ Total abdominal fat and retroperitoneal fat No effects on BW CN and HN groups: No effects on visceral adiposity % No effects on plasma TG No effects on plasma TCNo improvement in GT & IT No effects on systolic BP	HN: ↓ Hepatic fat vacuole size CN and HN groups: ↑ Abundance of Oxyphotobacteria	[46]
Male Wistar rat (3 weeks old)	*Tisochrysis lutea* powder (12%) 8 weeks	CTRL: Standard diet HF: 260 High fat diet with 10% fructose in drinking water HF-Tiso: HF diet + *T. lutea* powder	HF-Tiso: ↓ BW ↓ AAT and EAT weight/ BW ratio ↓ Plasma TG ↑ Plasma HDL-C ↓ Plasma LDL-C ↓ Plasma glucose ↓ HOMA-IR index	HF-Tiso: ↓ Plasma insulin ↓ Plasma TNF-α ↑ Adipose tissue anti-inflammatory IL-10 ↓ AIP ↓ Serum LPS ↓ Leptin ↓ TG in liver ↓ TC in liver	[6]
Mixed sex and breed of horse	DHA-rich microalgae (110	Control horses Treated horses	Treated horses: No effects on BW No effect on	↑ Plasma DHA ↓ TNF-α MFI	[47]

Animal Model	Microalgae and Doses	Experimental Design	Effects on MetS	Mechanisms	Reference Number
(treatment group is 13.2 ± 4.4 years old and control group is 11.5 ± 2.6 years old)	g/horse/d) 46 days		cresty neck score ↓ Plasma TG No effects on glucose tolerance		
Male Wistar rat (3 weeks old)	*Phaeodactylum tricornutum* powder (12%) 8 weeks	CTRL: Control group fed with standard diet HF: 260 High fat diet with 10% fructose in drinking water HF-Phaeo: HF diet + *P. tricornutum* powder	HF-Phaeo: ↓ BW ↓ AAT and EAT weight/ BW ratio ↓ Plasma TC ↓ Plasma TG ↑ Serum HDL-C ↓ HOMA-IR index No effects on plasma glucose	HF-Phaeo: ↓ Plasma insulin ↑ n-3 LC-PUFA levels in plasma, RBC, and liver lipids ↑ Δ9-Desaturase level in liver lipids ↓ Liver weight/ BW ratio ↓ MUFA levels in plasma lipid and liver phospholipids ↓ TG in liver ↓ TC in liver ↓ AIP ↓ Plasma TNF-α and IL-6 ↑ Plasma IL-4 and IL-10 ↓ Plasma leptin	[10]
Sprague Dawley rat(8 weeks old)	*Coccomyxa gloeobotrydiformis* (CGD) (100 mg/kg BW/d) 12 weeks	Control: Standard chow diet NC: High-energy diet without MetS MS: High-energy diet with MetS MS+CGD: High-energy diet with MetS + CDG MS + CVD: High-energy diet with MetS and CVD MS + CVD + CGD: High-energy diet with	MS + CGD: ↓ BW ↓ AC ↓ Serum glucose level ↓ SBP ↓ Serum TG and LDL-C levels ↑ Serum HDL-C levels MS + CVD + CGD: ↑ Left ventricular systolic and end diastolic pressure, and left ventricular systolic pressure	MS + CGD: ↑ AMPK and PGC-1α gene expressions in heart, adipose and skeletal muscle tissues ↑ MRC coenzymes (ATPase 6, cytochrome b and SDHA) gene expressions in the liver, heart and skeletal muscle ↓ UCP2 gene expression MS + CVD + CGD: ↓ Pro-inflammatory	[48]

genesis 23, 189–230.

2. Ghee, L.K.; Kooi, C.W. A Review of Metabolic Syndrome Research in Malaysia. Med. J. Malays. 2016, 71, 19–27.

Animal Model	Microalgae and Doses	Experimental Design	Effects on MetS	Mechanisms	Reference Number
		MetS and CVD + CGD	maximum increase rate and diastolic pressure maximum decrease rate	TNF-α and MDA gene expressions in myocardial tissue ↑ SOD gene expression in myocardial tissue ↑ Bcl-2 gene expression ↓ Bax gene and cleaved caspase-3 gene expressions were decreased ↑ TMOD1 gene expression	

The marine microalga, tisochrysis lutea, protects against metabolic disorders associated with metabolic syndrome and obesity. Nutrients 2021, 13, 430.

AAT: abdominal adipose tissue, AC: abdominal circumference, ACDC: adiponectin, AIP: atherogenic index of plasma, ALT: alanine transaminase, AMPK: adenosine monophosphate-activated protein kinase, AST: aspartate transaminase, ATPase 6: adenosine triphosphatase 6, Bcl-2: B-cell lymphoma 2, BW: body weight, EAT: epididymal adipose tissue, FOXP3: forkhead box P3, GCLm: glutamate-cysteine ligase modifier subunit, GHS-S: GSH synthetase, GPx: glutathione peroxidase, GPx1: glutathione peroxidase 1, GR: glutathione reductase, GSH: glutathione, GT: glucose tolerance, HDL-C: high-density lipoprotein cholesterol, HMOX1: Heme oxygenase 1, HOMAR-IR: Homeostatic Model Assessment of Insulin Resistance, IFNG: interferon gamma, IL-10: interleukin-10, IL-1β: interleukin 1 beta, IL-4: interleukin-4, IL-6: interleukin-6, IR: insulin resistance, IT: insulin tolerance, LDL-C: low-density lipoprotein cholesterol, LPS: lipopolysaccharides, MDA: malondialdehyde, MFI: mean fluorescence intensity, MRC: mitochondrial respiratory chain, MUFA: monounsaturated fatty acids, NEFA: non-esterified fatty acids, NF-κB: nuclear factor kappa B subunit 1, NOx: nitric oxide metabolites, NRF2: nuclear factor erythroid 2-related factor 2, oxLDL: oxidized low-density lipoprotein, PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha, RBC: red blood cell, SBP: systolic blood pressure, SDHA: succinate dehydrogenase complex, subunit-A, SOD: superoxide dismutase, SOD1: superoxide dismutase 1, SOD2: superoxide dismutase 2, TC: total cholesterol, TG: triglyceride, TGFβ1: transforming growth factor beta-1, TMOD1: Tropomodulin 1, TNFα: tumor necrosis factor alpha, UCP2: uncoupling protein 2, VLDL-C: very low-density lipoprotein cholesterol.

7. Wong, S.K.; Ramli, F.F.; Ali, A.; Ibrahim, N.I. Genetics of Cholesterol-Related Genes in Metabolic Syndrome: A Review of Current Evidence. Biomedicines 2022, 10, 3239.
8. di Marzo, V.; Silvestri, C. Lifestyle and metabolic syndrome: Contribution of the endocannabinoidome. Nutrients 2019, 11, 1956.
9. Nilsson, P.M.; Tuomilehto, J.; Rydén, L. The metabolic syndrome–What is it and how should it be managed? Eur. J. Prev. Cardiol. 2019, 26, 33–46.
10. Mayer, C.; Côme, M.; Ulmann, L.; Zittelli, G.C.; Faraloni, C.; Nazih, H.; Ouguram, K.; Chénais, B.; Mimouni, V. Preventive effects of the marine microalga phaeodactylum tricornutum, used as a food supplement, on risk factors associated with metabolic syndrome in wistar rats. Nutrients 2019, 11, 1069.
11. Laamanen, C.A.; Desjardins, S.M.; Senhorinho, G.N.A.; Scott, J.A. Harvesting microalgae for health beneficial dietary supplements. Algal Res. 2021, 54, 102189.
12. Vale, M.A.; Ferreira, A.; Pires, J.C.M.; Gonçalves, G.A.L. CO2 capture using microalgae. In Advances in Carbon Capture; Methods, Technologies and Applications; Woodhead Publishing: Sawston, UK, 2020; pp. 381–405.
13. Eltanahy, E.; Torky, A. Microalgae as Cell Factories: Food and Feed-grade High-value Metabolites. In Microalgal Biotechnology: Recent Advances, Market Potential, and Sustainability; Shekh, A., Schenk, P., Sarada, R., Eds.; The Royal Society of Chemistry: London, UK, 2021.
14. de Oliveira, A.P.F.; Bragotto, A.P.A. Microalgae-Based Products: Food and Public Health. Future Foods 2022, 6, 100157.
15. Ampofo, J.; Abbey, L. Microalgae: Bioactive Composition, Health Benefits, Safety and Prospects as Potential High-Value Ingredients for the Functional Food Industry. Foods 2022, 11, 1744.

16. 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.
17. Nethravathy, M.U.; Mehar, J.G.; Mudliar, S.N.; Shekh, A.Y. Recent Advances in Microalgal Bioactives for Food, Feed, and Healthcare Products: Commercial Potential, Market Space, and Sustainability. Compr. Rev. Food Sci. Food Saf. 2019, 18, 1882–1897.
18. Mourelle, M.L.; Gómez, C.P.; Legido, J.L. Cosmetics the Potential Use of Marine Microalgae and Cyanobacteria in Cosmetics and Thalassotherapy. Cosmetics 2017, 4, 46.
19. Yarkent, Ç.; Gürlek, C.; Oncel, S.S. Potential of microalgal compounds in trending natural cosmetics: A review. Sustain. Chem. Pharm. 2020, 17, 100304.
20. Ramos-Romero, S.; Torrella, J.R.; Pagès, T.; Viscor, G.; Torres, J.L. Edible Microalgae and Their Bioactive Compounds in the Prevention and Treatment of Metabolic Alterations. Nutrients 2021, 13, 563.
21. Schoch, C.L.; Ciufo, S.; Domrachev, M.; Hotton, C.; Kannan, S.; Khovanskaya, R.; Leipe, D.; Mcveigh, R.; O'Neill, K.; Robbertse, B.; et al. NCBI Taxonomy: A comprehensive update on curation, resources and tools. Database 2020, 2020, baaa062.
22. Sæther, T.; Paulsen, S.M.; Tungen, J.E.; Vik, A.; Aursnes, M.; Holen, T.; Hansen, T.V.; Nebb, H.I. Synthesis and biological evaluations of marine oxohexadecenoic acids: PPARα/γ dual agonism and anti-diabetic target gene effects. Eur. J. Med. Chem. 2018, 155, 736–753.
23. Chen, W.; Zhou, X.B.; Liu, H.Y.; Xu, C.; Wang, L.L.; Li, S. P633H, a novel dual agonist at peroxisome proliferator-activated receptors α and γ, with different anti-diabetic effects in db/db and KK-A y mice. Br. J. Pharmacol. 2009, 157, 724–735.
24. Brown, J.D.; Plutzky, J. Peroxisome proliferator-activated receptors as transcriptional nodal points and therapeutic targets. Circulation 2007, 115, 518–533.
25. Moldes-Anaya, A.; Sæther, T.; Uhlig, S.; Nebb, H.I.; Larsen, T.; Eilertsen, H.C.; Paulsen, S.M. Two Isomeric C16 Oxo-Fatty Acids from the Diatom Chaetoceros Karianus Show Dual Agonist Activity towards Human Pe-roxisome Proliferator-Activated Receptors (PPARs) α/γ. Mar. Drugs 2017, 15, 148.
26. Massaro, M.; Scoditti, E.; Pellegrino, M.; Carluccio, M.A.; Calabriso, N.; Wabitsch, M.; Storelli, C.; Wright, M.; de Caterina, R. Therapeutic potential of the dual peroxisome proliferator activated receptor (PPAR)α/γ agonist aleglitazar in attenuating TNF-α-mediated inflammation and insulin resistance in human adipocytes. Pharmacol. Res. 2016, 107, 125–136.
27. Nakamura, M.T.; Yudell, B.E.; Loor, J.J. Regulation of energy metabolism by long-chain fatty acids. Prog. Lipid Res. 2014, 53, 124–144.

28. Kim, M.; Furuzono, T.; Yamakuni, K.; Li, Y.; Kim, Y.L.; Takahashi, H.; Ohue-Kitano, R.; Jheng, H.F.; Takahashi, N.; Kano, Y.; et al. 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, enhances energy metabolism by activation of TRPV1. FASEB J. 2017, 31, 5036–5048.
29. Goto, T.; Kim, Y.L.; Furuzono, T.; Takahashi, N.; Yamakuni, K.; Yang, H.E.; Li, Y.; Ohue, R.; Nomura, W.; Sugawara, T.; et al. 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, potently activates PPARγ and stimulates adipogenesis. Biochem. Biophys. Res. Commun. 2015, 459, 597–603.
30. Hira, T.; Ogasawara, S.; Yahagi, A.; Kamachi, M.; Li, J.; Nishimura, S.; Sakaino, M.; Yamashita, T.; Kishino, S.; Ogawa, J.; et al. Novel Mechanism of Fatty Acid Sensing in Enteroendocrine Cells: Specific Structures in Oxo-Fatty Acids Produced by Gut Bacteria Are Responsible for CCK Secretion in STC-1 Cells via GPR40. Mol. Nutr. Food Res. 2018, 62, 1800146.
31. Gao, H.; Geng, T.; Huang, T.; Zhao, Q. Fish Oil Supplementation and Insulin Sensitivity: A Systematic Review and Meta-Analysis. Lipids Health Dis. 2017, 16, 131.
32. Padanad, M.S.; Konstantinidou, G.; Venkateswaran, N.; Melegari, M.; Rindhe, S.; Mitsche, M.; Yang, C.; Bat-ten, K.; Huffman, K.E.; Liu, J.; et al. Fatty Acid Oxidation Mediated by Acyl-CoA Synthetase Long Chain 3 Is Required for Mutant KRAS Lung Tumorigenesis. Cell Rep. 2016, 16, 1614–1628.
33. Ortega-Senovilla, H.; van Poppel, M.N.M.; Desoye, G.; Herrera, E. Angiopoietin-like protein 4 (ANGPTL4) is related to gestational weight gain in pregnant women with obesity. Sci. Rep. 2018, 8, 12428.
34. Kersten, S. Role and mechanism of the action of angiopoietin-like protein ANGPTL4 in plasma lipid metabolism. J. Lipid Res. 2021, 62, 100150.
35. Xu, A.; Lam, M.C.; Chan, K.W.; Wang, Y.; Zhang, J.; Hoo, R.L.C.; Xu, J.Y.; Chen, B.; Chow, W.-S.; Tso, A.W.K.; et al. Angiopoietin-like protein 4 decreases blood glucose and improves glucose tolerance but induces hyperlipidemia and hepatic steatosis in mice. Proc. Natl. Acad. Sci. USA 2005, 102, 6086–6091.
36. Zhang, S.; Liu, G.; Xu, C.; Liu, L.; Zhang, Q.; Xu, Q.; Jia, H.; Li, X.; Li, X. Perilipin 1 mediates lipid metabolism homeostasis and inhibits inflammatory cytokine synthesis in bovine adipocytes. Front. Immunol. 2018, 9, 467.
37. Ma, X.; Lee, P.; Chisholm, D.J.; James, D.E. Control of adipocyte differentiation in different fat depots; Implications for pathophysiology or therapy. Front. Endocrinol. 2015, 6, 1.
38. Prentice, K.J.; Saksi, J.; Hotamisligil, G.S. Adipokine FABP4 integrates energy stores and counterregulatory metabolic responses. J. Lipid Res. 2019, 60, 734–740.

39. Hanschkow, M.; Boulet, N.; Kempf, E.; Bouloumié, A.; Kiess, W.; Stein, R.; Körner, A.; Landgraf, K. Expression of the Adipocyte Progenitor Markers MSCA1 and CD36 is Associated with Adipose Tissue Function in Children. J. Clin. Endocrinol. Metab. 2022, 107, E836–E851.
40. Liu, X.; Strable, M.S.; Ntambi, J.M. Stearoyl CoA desaturase 1: Role in cellular inflammation and stress. Adv. Nutr. 2011, 2, 15–22.
41. Armani, A.; Berry, A.; Cirulli, F.; Caprio, M. Molecular mechanisms underlying metabolic syndrome: The expanding role of the adipocyte. FASEB J. 2017, 31, 4240–4255.
42. Kahn, C.R.; Wang, G.; Lee, K.Y. Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome. J. Clin. Investig. 2019, 129, 3990–4000.
43. Gil-Cardoso, K.; del Bas, J.M.; Caimari, A.; Lama, C.; Torres, S.; Mantecón, L.; Infante, C. TetraSOD®, a Unique Marine Microalgae Ingredient, Promotes an Antioxidant and Anti-Inflammatory Status in a Metabolic Syndrome-Induced Model in Rats. Nutrients 2022, 14, 4028.
44. Lugarà, R.; Renner, S.; Wolf, E.; Liesegang, A.; Bruckmaier, R.; Giller, K. Crossbred Sows Fed a Western Diet during Pre-Gestation, Gestation, Lactation, and Post-Lactation Periods Develop Signs of Lean Metabolic Syndrome That Are Partially Attenuated by Spirulina Supplementation. Nutrients 2022, 14, 3574.
45. Mayer, C.; Côme, M.; Ulmann, L.; Martin, I.; Zittelli, G.C.; Faraloni, C.; Ouguerram, K.; Chénais, B.; Mimouni, V. The Potential of the Marine Microalga Diacronema lutheri in the Prevention of Obesity and Metabolic Syndrome in High-Fat-Fed Wistar Rats. Molecules 2022, 27, 4246.
46. du Preez, R.; Majzoub, M.E.; Thomas, T.; Panchal, S.K.; Brown, L. Nannochloropsis oceanica as a microalgal food intervention in diet-induced metabolic syndrome in rats. Nutrients 2021, 13, 3991.
47. Elzinga, S.E.; Betancourt, A.; Stewart, J.C.; Altman, M.H.; Barker, V.D.; Muholland, M.; Bailey, S.; Brennan, K.M.; Adams, A.A. Effects of Docosahexaenoic Acid–Rich Microalgae Supplementation on Metabolic and Inflammatory Parameters in Horses With Equine Metabolic Syndrome. J. Equine Vet. Sci. 2019, 83, 102811.
48. Zheng, N.; Ding, X.; Wei, D.; Dai, B.; Zheng, L.; Sumi, R.; Hu, D.; Jahane, R.; Sun, L. Therapeutic effects of coccomyxagloeobotrydiformis on the metabolic syndrome in rats. Cell. Physiol. Biochem. 2018, 48, 1519–1529.