CHAPTER EIGHT

Seaweed-derived bioactives as potential energy regulators in obesity and type 2 diabetes

Giovanna Bermano[a,†], Teodora Stoyanova[a], Franck Hennequart[b], Cherry L. Wainwright[a,*,†]

[a]Centre for Natural Products in Health, School of Pharmacy & Life Sciences, Robert Gordon University, Aberdeen, United Kingdom
[b]R&D Department, Algaia, Saint-Lô, France
*Corresponding author: e-mail address: c.wainwright@rgu.ac.uk

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Abstract

There is epidemiological evidence that dietary intake of seaweeds is associated with a lower prevalence of chronic diseases. While seaweeds are of high nutritious value, due to their high content of fiber, polyunsaturated fatty acids and minerals, they also contain an abundance of bioactive compounds. There is a growing body of scientific data that these bioactive moieties exert effects that could correct the metabolic dysregulation that is present in obesity and Type 2 diabetes (T2D). In this review we describe how

† These authors share co-senior authorship.

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the molecular mechanisms, specific to different tissues, that underly obesity and T2D are influenced by both seaweed extracts and seaweed-derived bioactive molecules. In obesity, modulation of antioxidant capacity and reduction of intracellular ROS levels within tissues, and regulation of signaling pathways involved in enhancing browning of white adipose tissue, have been highlighted as key mechanism and identified as a potential target for optimal energy metabolism. In T2D, management of post-prandial blood glucose by modulating α-glucosidase or α-amylase activities, modulation of the AMPK signaling pathway, and similarly to obesity, reduction of ROS and NO production with subsequent increased expression of antioxidant enzymes have been shown to play a key role in glucose metabolism and insulin signaling. Future studies aimed at discovering new therapeutic drugs from marine natural products should, therefore, focus on bioactive compounds from seaweed that exert antioxidant activity and regulate the expression of key signaling pathways involved in glucose homeostasis, mechanisms that are common to both obesity and T2D management. In addition, more data is required to provide evidence of clinical benefit.

Abbreviations

3T3-LI	adipocyte cell line
ACC	acyl-coA carboxylase
AGE's	advanced glycation end-products
Akt/PKB	protein kinase B
AMPK	AMP-activated protein kinase
BAT	brown adipose tissue
BMI	body mass index
C/EBP-α/β	CCAAT/enhancer-binding proteins α/β
cAMP	cyclic adenine monophosphate
CCK	cholecystokinin
COX-2	cyclooxygenase-2
CPT1a	carnitine palmitoyltransferase-1a
DPP-4	dipeptidyl peptidase-4
EER	energy efficiency ratio
ERK	extracellular signal-regulated kinases
FABP4	fatty acid binding protein 4
FAS	fatty acid synthase
G6PDH	glucose-6-phosphate dehydrogenase
GAE	gallic acid equivalents
GLP-1	glucagon-like peptide-1
GLUT-4	glucose transporter type 4
GSH	glutathione
IL-6	interleukin-6
iNOS	inducible nitric oxide synthase
IRS-1	insulin receptor substrate
JNK	Jun N-terminal kinase
K_{ATP}	ATP-sensitive potassium channels

MAPK	mitogen activated protein kinase
MCP-1	monocyte chemoattractant protein-1
Nox4	nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase 4
NQO1	NAD(P)H quinone oxidoreductase1
PAI-1	plasminogen activator inhibitor-1
PEPCK	phosphoenolpyruvate carboxykinase
PI3K	phosphatidylinositol 3-kinases
PPAR-γ	peroxisome proliferator-activated receptor-γ
PTP1B	protein-tyrosine phosphatase 1B
PYY	peptide YY
ROS	reactive oxygen species
SCD1	stearoyl-coenzyme A desaturase-1
SREBP-1C	sterol regulatory element binding protein 1c
SUR1	subunit sulfonylurea receptor 1
T2D	type 2 diabetes
TBARS	thiobarbituric acid reactive substances
TNFα	tumor necrosis factor alpha
UCP2	uncoupling protein 2
WAT	white adipose tissue

1. Introduction

Globally, obesity has reached epidemic proportions and it is contributing significantly to the problem of chronic diseases such as insulin resistance, type 2 diabetes mellitus, heart-related diseases, certain cancers, osteoarthritis, and sleep apnoea (Barness, Opitz, & Gilbert-Barness, 2007; Berrington de Gonzalez et al., 2010). It results from an imbalance between caloric intake and expenditure and is characterized by a disproportionate accumulation of adipose tissue that is commonly accompanied by systemic inflammation (Gonzalez-Muniesa et al., 2017). As obesity possesses different etiological and pathological origins, no single treatment or drug can effectively control the condition (Bakhai & Tirgar, 2013).

One of the major metabolic consequences of obesity is the development of Type 2 diabetes (T2D). In contrast to Type 1 diabetes, in which the destruction of pancreatic β-cells results in failure of insulin secretion and can only be treated by insulin replacement therapy, T2D results from reduced insulin secretion and/or insulin resistance and is open to therapeutic management by pharmacological means. A description of

the physiological control of glucose and the development of insulin resistance is outside the scope of this review and has been well described elsewhere (e.g., Petersen & Shulman, 2018), but the main pharmacological approaches for the management of T2D involve the use of agents that target key events, from the point of entry of glucose into the circulation to the responsiveness to insulin at the cellular level. However, many of the drugs currently used for the management of T2D are associated with unpleasant side effects, and despite the variety of drugs available many do not achieve the appropriate glycemic control (Pramanik, Rathwa, Patel, Ramachandran, & Begum, 2018).

Seaweeds are of significant nutritious value due to their high content of fiber, polyunsaturated fatty acids and minerals, but they also contain an abundance of bioactive compounds. There is epidemiological evidence that in geographical regions (e.g., Japan and Korea) where the dietary intake of seaweeds is high, the prevalence of chronic diseases (e.g., hyperlipidemia, cardiovascular disease and cancer) is lower (Brown et al., 2014) and there is a growing body of scientific data that bioactive molecules present in seaweed (e.g., polyunsaturated fatty acids and phenolic compounds) exert effects that could correct the metabolic dysregulation that is present in obesity and T2D (Sharifuddin, Chin, Lim, & Phang, 2015; Wan-Loy & Siew-Moi, 2016). The cellular mechanisms underlying these biological effects, and the identity of the bioactive molecules responsible for the various pharmacological actions, are beginning to emerge. In this review we provide an up-to-date summary of how seaweed-derived bioactives may provide the basis for the development of novel therapeutics for the management of obesity and/or T2D.

2. Metabolic effects of seaweed in obesity

There are two main categories of anti-obesity drugs: ones that are able to reduce or limit energy absorption and those that aim to decrease fat mass by increasing energy expenditure or redistributing adipose tissue. Existing drugs have not been able to significantly and successfully reduce weight, and, as such, there is an urgent need for safe anti-obesity drugs that are therapeutically potent, and for research aimed at identifying their mechanism of action and at supporting the lack of side effects (Yun, 2010). One aspect of this research has focused on discovering extracts and/or bioactives with anti-obesity properties from the marine environment that might be readily available and have less adverse effects. Whole seaweed meal or seaweed

extracts have been the focus of several studies; however, their mode of action in preventing fat accumulation and/or reducing weight is not totally understood; neither the classes of compounds nor the active ingredients responsible for seaweed anti-obesity properties have been fully characterized.

This section aims to provide a mechanistic evidence of the activity of whole seaweeds and extracts on metabolic physiology at the whole body level and highlight potential therapeutic targets at organ/tissue level. Scientific studies assessing the activity of whole seaweed, extracts or main bioactives via clinical trials, animal models or cell systems have been reviewed in the following sections and presented according to whole body or targeted tissues.

2.1 Activity of seaweed extracts and bioactive compounds at the whole-body level

Several animal studies have been undertaken over the years to test the anti-obesity properties of seaweeds and their extracts in mice or rats fed an obesogenic high-fat diet. Brown seaweeds have been widely studied, mainly because of their use as a food source in Far East Asian countries and Western Europe. Their high content in dietary fibers, minerals and vitamins, and low fat content, have made them interesting from a nutritional perspective, but they also offer a rich source of bioactive compounds, including complex polysaccharides (e.g., alginates, fucoidan and laminarin), polyphenols and phlorotannins, carotenoids such as fucoxanthin, and polyunsaturated fatty acids (Afonso, Catarino, Silva, & Cardoso, 2019), which can provide new sources of potential therapeutic drugs (Unnikrishnan & Jayasri, 2018).

2.1.1 Whole seaweed and seaweed extracts

The effect of the brown seaweed *Sargassum polycystum* on body weight and plasma biomarkers has been studied in rats fed a high fat diet supplemented with different doses of the seaweed powder for 8 weeks. The high-fat diet supplemented with 10% seaweed powder decreased the levels of plasma total cholesterol and triglycerides (35% and 45% vs high-fat control diet, respectively) and had a positive effect on the inhibition of weight gain (78% vs high-fat control diet) (Awang et al., 2014). Similarly, the effect of seamustard (*Undaria pinnatifida*) intake on body weight gain, blood glucose level and lipid profiles were studied in rats fed diets with different energy nutrient compositions (high fat vs high carbohydrate). Food intake, body weight gain and energy efficiency ratio (EER) were reduced in the high fat diet supplemented with 10% seamustard group (HFM10) compared with animals fed a high carbohydrate diet with 5% seamustard (HCM5). Fecal cholesterol

excretion and serum LDL-cholesterol concentration in HFM10 group were the highest, while serum HDL-cholesterol level was the lowest among groups. Interestingly, HDL-cholesterol concentration was the highest in HCM5 group among groups. From these results, it was suggested that seamustard intake might be more effective for body weight control, more so with a high-fat diet than a high carbohydrate diet, but not for improving blood lipid profiles (Shin, 2009). Seaweed extract of *Ascophyllum nodosum*, ID-alG™, administered for 9 weeks to high-fat-fed Sprague-Dawley rats at a concentration of 40 and 400 mg/kg/day improved significantly the mean body weight gains and decreased significantly the percentage of body fat mass of rats (−9.8% and −19.0%), in comparison to high-fat diet fed rats. In the same way, triglyceride blood level was also significantly improved for the dose of 400 mg/kg/day (−30.6% vs +49.9% for the positive control); whereas total cholesterol, LDL and HDL blood levels were not modified (Terpend, Bisson, Le Gall, & Linares, 2012).

Fewer studies have investigated the response to green seaweeds in animal models of obesity and/or metabolic syndrome. Food supplementation with 5% dried *Ulva ohnoi* (UO) and *Derbesia tenuissima* (DT) for 8 weeks showed that UO lowered total final body fat mass by 24%, systolic blood pressure by 29 mmHg, and improved glucose utilization and insulin sensitivity. In contrast, DT did not change total body fat mass but decreased plasma triglycerides by 38% and total cholesterol by 17%. The different composition of the two seaweeds especially in relation to soluble fiber (UO contained 18.1% soluble fiber as part of 40.9% total fiber, while DT contained 23.4% total fiber, essentially as insoluble fiber) may justify why UO was more effective in reducing metabolic syndrome than DT (Kumar, Magnusson, Ward, Paul, & Brown, 2015).

2.1.2 Complex polysaccharides

Bioactive compounds extracted from brown seaweed have also been shown to exert anti-obesity properties. In particular, the hypolipidemic activity of a fucoidan extracted from the brown seaweed *Sargassum henslowianum* was tested in a mouse model of obesity: oral administration of the fucoidan at 100 mg/kg/day decreased blood cholesterol, triglyceride and LDL-cholesterol levels by 20% compared to obese mice administered water instead of seaweed extracts (Cuong, Thuy, Huong, Ly, & Van, 2015). Laminarin, a type of β-glucan isolated from brown seaweeds, affected energy homeostasis in obese mice orally administrated with laminarin. Chronic intragastric administration of laminarin (1 g/kg) every 2 days for 4 weeks

decreased high fat-diet-induced body weight gain and fat deposition, and reduced blood glucose level and glucose tolerance; whereas acute laminarin administration (one single dose of 1 g/kg) enhanced serum glucagon-like peptide-1 (GLP-1) content, and suppressed food intake of mice after 3 h (Yang et al., 2017). The anti-obesity effects of enzymatic-digested alginate oligomers (E-AO) obtained from IL-6M and ULV-L3 (trade name of alginate products prepared from *Durvillaea* species and *Lessonia nigrescens*, respectively) were investigated at a 10% concentration in male mice fed a high-fat diet. E-AO showed strong anti-obesity effects judged by the reduction in body and adipose tissue weights (23% decrease in body weight gain and 40% decrease in epididymal fat weigh compared to mice fed high-fat diet). In addition, they suppressed plasma leptin level in females (Nakazono et al., 2016). Extracts from *Gelidium amansii* (GA) obtained by ethanol extraction were administered to male C57BL/6 mice in addition to a high fat diet, for 12 weeks. *G. amansii* extract (GAE) had protective effects: body weight was greatly decreased in mice fed a high-fat diet and supplemented with 1% or 3% GAE; blood glucose and serum insulin levels were also reduced by GAE treatment, suggesting improvement in glucose metabolism. GAE supplementation also led to a significant decrease in total cholesterol and triglyceride levels. Furthermore H&E staining confirmed smaller adipocytes size in mice fed a high-fat diet supplemented with GAE and reduced levels of steatosis in the liver (Kang et al., 2016).

From the studies highlighted above and summarized in Table 1, it is evident that, at least in animal models of obesity, whole seaweed or bioactive compounds prevent body weight gain and ameliorate plasma lipid profile and glucose metabolism; however the mechanisms by which they do so have not been fully defined. Changes in lipid absorption at the gastro-intestinal level, in glucose homeostasis and/or in leptin secretion/action may be partly responsible for the anti-obesity effects.

2.1.3 Human studies

Despite the number of studies carried out in animals, clinical studies are limited and do not encompass the assessment of potential mechanisms of action. Few studies have assessed alginates for their potential role in energy regulation through the inhibition of energy intake and/or an increase in the feeling of satiety. Postprandial satiety, energy intake, and gastric emptying rate (GER) were studied in normal-weight subjects via a four-way placebo-controlled, double-blind, crossover trial, who were randomly assigned to receive a 3% preload concentration of either low volume (LV; 9.9 g alginate in 330 mL)

Table 1 Summary of the anti-obesity effects of seaweed bioactives.

Seaweed color	Seaweed species	Country of origin	Extracts/specific compounds (concentration)	Biological model	Action	Reference source
Whole body						
Brown	*Ascophyllum nodosum*		Extract—ID-alG™—Bioserae (40, 400 mg/kg/day)	Female Sprague-Dawley rats fed high-fat diet	↓ Weight gain, body fat mass, plasma triglycerides	Terpend et al. (2012)
Brown	*Durvillaea* species *Lessonia nigrescens*	South Korea	Alginates oligomers enzymatically digested (IL-6M and ULV-L3 trade name) (10% w/w)	Male and female ddY mice fed high-fat diet	↓ Body weight gain, adipose tissue weight ↓ Plasma leptin levels in female mice	Nakazono et al. (2016)
Red	*Gelidium amansii*	South Korea	Ethanol extract (1%, 3% w/w)	Male C57BL/6 mice fed high-fat diet	= Body weight gain, adipose tissue weight with 1% ↓ Body weight gain, adipose tissue weight, serum total cholesterol, triglyceride with 3% ↓ Adipocytes size, steatosis in liver	Kang et al. (2016)
Brown	*Laminaria digitata*		Alginate (CM3 from Mayo Research Pharmacy)	Male and female healthy overweight/obese American adult volunteers	= Gastric functions, satiation, appetite, and gut hormones (ghrelin, CCK, GLP-1, PYY)	Odunsi et al. (2010)
Brown	*Laminaria hyperborea Lessonia trabeculata*		Alginate (Algogel DPG JO; Cargill) (low volume (LV) = 9.9 g sodium alginate/330 mL water; high volume (HV) = 15 g sodium alginate/500 mL water)	Male and female healthy young Danish subjects	↓ Energy intake with LV = Satiety feelings with LV ↑ Satiety feelings with HV ↓ Hunger, feeling of prospective food consumption with HV	Georg Jensen, Kristensen, Belza, Knudsen, and Astrup (2012)
Brown	*Sargassum henslowianum*	Vietnam	Fucoidan (100 mg/kg/day)	BALB/c strain mice fed high-fat diet	↓ Body weight, cholesterol, triglyceride, LDL-cholesterol	Cuong et al. (2015)

Brown	*Sargassum polycystum*	Malaysia	Whole seaweed powder (10% w/w)	Male Sprague-Dawley rats fed high-fat diet	↓ Weight gain, plasma total cholesterol, triglycerides	Awang et al. (2014)
Brown	*Undaria pinnatifida* (Seamustard)	Korea	Whole seaweed powder (5%, 10% w/w)	Male Sprague-Dawley rats fed high-fat diet or high carbohydrate diet	↓ Food intake, body weight gain, EER in HFM10 vs HCM5 ↑ Fecal cholesterol excretion, serum LDL-cholesterol in HFM10 ↓ Serum HDL-cholesterol level in HFM10	Shin (2009)
Brown			Fucoxanthin (1 and 3 mg/day)	Male and female healthy Japanese obese subjects	↓ Relative (ratio versus before treatment) body weight, BMI, visceral fat area in 3 mg/day group ↓ Relative total fat mass, subcutaneous fat area, waist circumference = Blood pressure, pulse rate, blood parameters, urinalysis	Hitoe and Shimoda (2017)
Brown			Laminarin (1 g/kg)	C57/BL6 mice fed high-fat diet	↓ Body weight, body weight gain, feeding efficiency = Food intake ↑ Serum GLP-1, in acute administration	Yang et al. (2017)
Green	*Derbesia tenuissima*	Australia	Dried seaweed (5% w/w)	Wistar rats fed a high carbohydrate/high-fat diet	= Total body fat mass ↓ Plasma triglycerides	Kumar et al. (2015)
Green	*Ulva ohnoi*	Australia	Dried seaweed (5% w/w)	Wistar rats fed a high carbohydrate/high-fat diet	↓ Total body fat mass, systolic blood pressure	Kumar et al. (2015)

BMI, body mass index; *CCK*, cholecystokinin, *EER*, energy efficiency ratio; *GLP-1*, glucagon-like peptide-1; *HCM5*, a high carbohydrate diet with 5% seamustard; *HFM10*, high-fat diet supplemented with 10% seamustard; *PYY*, peptide YY.

or high volume (HV; 15.0 g alginate in 500 mL) alginate-based beverage (Algogel DPG JO; Cargill, Minneapolis, MN, a combination of extracts from brown seaweeds *Laminaria hyperborea* and *Lessonia trabeculata*), or an iso-volume placebo beverage, 30 min before a fixed breakfast and again before an ad libitum lunch. Consumption of LV-alginate preload induced an 8.0% reduction in energy intake compared to the placebo beverage at the following lunch meal, without differences in satiety. The HV alginate significantly increased satiety, reduced hunger and the feeling of prospective food consumption compared to the placebo, suggesting that alginate consumption does affect satiety and energy intake (Georg Jensen et al., 2012). On the contrary, a study evaluating the effects of 10 days treatment with alginate (CM3 alginate-based on brown seaweed *Laminaria digitate*) or placebo on gastric functions, satiation, appetite, and gut hormones (ghrelin, cholecystokinin (CCK), GLP-1, peptide YY (PYY)), showed no effect on any of the variable measured questioning the potential use of short-term alginate treatment for weight loss (Odunsi et al., 2010).

In another study in which the effect of fucoxanthin (Fx) (1 or 3 mg daily) was tested in Japanese obese subjects, in a double-blind placebo-controlled study, administration of capsules containing Fx or placebo for 4 weeks induced a significant reduction of the relative (ratio versus before treatment) body-weight, BMI, and visceral fat area in the 3 mg/day Fx group compared to the placebo group. Relative values of total fat mass, subcutaneous fat area and waist circumference were also significantly lower in the 1 mg/day Fx group than the placebo group. No abnormalities in blood pressure, pulse rate, blood parameters, and urinalysis parameters were observed, thereby suggesting no adverse effects and supporting its potential use to improve a moderate overweight state by acting on both visceral and subcutaneous fat (Hitoe & Shimoda, 2017).

2.2 Activity of seaweed extracts and bioactive compounds in adipose tissue

The development of obesity is characterized by an increase in the number (hyperplasia) and size (hypertrophy) of adipocytes due to the processes of mitogenesis and differentiation, which are regulated by several factors, including genetic, endocrine, metabolic, environmental, and nutritional ones. Adipocyte function is associated with lipid homeostasis and energy balance: storing energy in the form of fatty acids, playing a central role in lipid and glucose metabolism and producing several hormones and cytokines (Rasouli & Kern, 2008). Targeting both adipogenesis and triglycerides

synthesis may have, therefore, promising outcomes in controlling adipose tissue growth and numerous metabolic disorders in obesity. Several anti-obesity medications, such as orlistat (Xenical), lorcaserin, and topiramate have been developed to combat adipose tissue growth and expansion; however, these medications are associated with various adverse effects and so suitable and safe alternatives are needed. Seaweed extracts and/or bioactive compounds from seaweed may thus play a role in modulating such processes and energy metabolism and several studies aimed to identify their efficacy, molecular mechanisms and molecular targets, have been carried out (summarized in Table 2), using the murine 3T3-L1 preadipocyte cell line to investigate adipogenesis and to study the differentiation processes of preadipocytes into adipocytes.

2.2.1 Whole seaweed and seaweed extracts

Extracts obtained by macerating brown seaweed *Sargassum oligocystum* (SE) and *Padina australis* (PE) using acetone, were applied to 3T3-L1 cells during the differentiation stage and during the mature stage of the adipocyte life cycle to assess the effects of extracts on adipogenesis and adipolysis. Application of SE at 12.5 and 50 μg/mL decreased adipogenesis by 71.7%, and 84.8%, respectively, while cells treated with 12.5 and 50 μg/mL PE showed 85.7%, and 89.0% adipogenesis, respectively, compared to control. Application of SE and PE to mature lipid cells stimulated adipolysis and the release of glycerol by up to 88.6% and 93.0%, respectively, with 12.5 and 50 μg/mL SE, while PE increased glycerol release up to 92.9% and 95.6% respectively, compared to isoproterenol, used as positive control (Jaswir et al., 2017). Fermentation of *Laminaria japonica* (LJF) was performed to increase its physiological activity, before screening its anti-obesity potential using 3T3-L1 adipocyte cells: LJF inhibited adipocyte differentiation by significantly reducing the expression levels of CCAAT/enhancer-binding proteins α/β (C/EBP-α/β) and peroxisome proliferator-activated receptor-γ (PPAR-γ), involved in the early and late stages of adipocyte differentiation, and by decreasing the concentration of the adipocytokine adiponectin (Kim & Jang, 2018). Seaweed extracts from 49 species were firstly tested for free radical scavenging properties and the 3 species containing the highest levels of polyphenols were tested on adipocyte differentiation and reactive oxygen species (ROS) production during adipogenesis in 3T3-L1 cells. High total phenol contents were observed in the extracts of *Ecklonia cava* (681.1 μg gallic acid equivalents (GAE)/g), *Dictyopteris undulata* (641.3 μg GAE/g), and *Laurencia intermedia* (560.9 μg GAE/g); whereas *Sargassum*

Table 2 Summary of the effects of seaweed bioactives on adipose tissue.

Seaweed color	Seaweed species	Country of origin	Extracts/specific compounds (concentration)	Biological model	Action	Reference source
Adipose tissue						
Green	*Caulerpa okamurae*	South Korea	Ethanol extract (25–500 μg/mL)	3T3-L1 Male C57BL/6 mice fed a high-fat diet	↓ Lipid accumulation (ORO staining) ↓ C/EBP-α, PPAR-γ, SREBP-1c proteins	Sharma, Kim, Kim, Park, and Rhyu (2017)
Green	*Caulerpa okamurae*	South Korea	Ethanol extract (250 mg/kg)	Male C57BL/6 mice fed a high-fat diet	↓ Weight gain markers such as free fatty acid, triglycerides, total cholesterol, glucose in plasma ↓ PPAR-γ, C/EBP-α, FAS, SRBP1c, acetyl-CoA synthetase proteins	Sharma et al. (2017)
Brown	*Ecklonia cava*	South Korea	Methanol extract (100 μg/mL) Dieckol (phlorotannin) (100 μM)	3T3-L1	↓ Adipogenesis (ORO staining) ↓ Adipogenesis (ORO staining) ↓ PPAR-γ, C/EBP-α, SREBP1, FABP4 mRNA and protein ↑ AMPK activation	
Brown	*Eisenia bicyclis*	South Korea	6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, dieckol, phlorofucofuroeckol A (phlorotannin) (10, 25 and 50 μg/mL) 6,6′-bieckol (50 μg/mL)	3T3-L1	↓ Lipid accumulation (ORO staining)—all phlorotannins ↓ PPAR-γ, C/EBP-α, SREBP-1c mRNA and protein—6,6′-bieckol ↓ FAS, ACC mRNA-6,6′-bieckol	Kwon et al. (2015)

Brown	*Fucus vesiculosus*	Brazil	Fucoidan rich fractions (different ratios fucose/glucuronic acid/galactose/xylose/sulfate—F0.5, F0.9, F1.1 and F2.0) (200 μg/mL)	3T3-L1	↑ Lipolysis (Glycerol release)—all fractions ↓ Adipogenesis (ORO staining)—F1.1, F2.0 ↑ Adipogenesis (ORO staining)—F0.5 ↓ C/EBP-α, C/EBP-β, PPAR-γ—F1.1, F2.0	Oliveira et al. (2018)
Brown	*Laminaria japonica*	South Korea	Extract from fermented seaweed	3T3-L1	↓ Adipocyte differentiation (C/EBP-α/β, PPAR-γ proteins) ↓ Adiponectin levels	Kim et al. (2018)
Brown	*Padina australis* *Sargassum oligocystum*	Malaysia	Acetone extract (12.5, 50 μg/mL)	3T3-L1	↓ Adipogenesis (ORO staining) ↑ Adipolysis (glycerol release)	Jaswir, Ahmad, Susanti, Bakhtiar, and Octavianti (2017)
Green Brown Brown Red	*Ulva* species *Palmaria palmata* *Undaria pinnatifida* *Himanthalia elongata*	Spain	Methanolic extracts (0.1 mg/mL)	3T3-L1	↓ Triacylglycerol levels	Rico et al. (2018)
Brown	*Sargassum echinocarpum*	Indonesia	Fucoxanthin	Pre-adipocyte cell from viscera tissue of wistar rats	↑ Adiponectin levels ↓ TNF-α expression	Firdaus, Nurdiani, and Prihanto (2015)

Continued

Table 2 Summary of the effects of seaweed bioactives on adipose tissue.—cont'd

Seaweed color	Seaweed species	Country of origin	Extracts/specific compounds (concentration)	Biological model	Action	Reference source
Brown	*Sargassum thunbergii*	Korea	Six indole derivatives (STCs) STC1: indole-2-carboxaldehyde STC-2: indole-3-carboxaldehyde STC-3: indole-4-carboxaldehyde STC-4: indole-5-carboxaldehyde STC-5: indole-6-carboxaldehyde STC-6: indole-7-carboxaldehyde (25, 50, 100 μM)	3T3-L1	↓ Adipocytes differentiation, lipid accumulation (ORO staining)—all STCs ↓ PPAR-γ, C/EBP-α, and SREBP-1c Protein—STC-1 and STC-5 ↓ AMPK activation and AMPK—STC-1 and STC-5	Kang et al. (2017)
Brown	*Undaria pinnatifida*	South Korea	Fucoidan (100 μg/mL)	3T3-L1	↓ Lipid accumulation (ORO staining) ↓ PPAR-γ, C/EBP-α, aP2 mRNA ↓ TNFα, MCP-1, PAI-1 ↓ ROS production	Kim and Lee (2012)
Brown	*Undaria pinnatifida*	Japan	Fucoxanthin (acetone extract) Fucoxanthinol (metabolite in white adipose tissue) (2.5 μM)	3T3-F442A adipocytes	↓ MCP-1 and IL-6 mRNA	Hosokawa et al. (2010)

Brown	*Undaria pinnatifida*	Japan	Fucoxanthin (acetone extract) (0.2% w/w)	C57Bl/6 and KK-A(y) mice	↓ WAT weight gain and hyperglycemia in KK-A(y) not C57Bl/6 mice ↓ MCP-1, TNF-α in MCP-1 in KK-A(y) not C57Bl/6 mice ↓ IL-6, PAI-1 mRNA in KK-A(y) mice	Hosokawa et al. (2010)
Brown	*Undaria pinnatifida*	South Korea	Fucoxanthin (ethanol extract) (0.2% w/w)	C57BL/6J mice fed high-fat diet	↓ WAT weights ↓ FA synthesis, ↓ UCP1 mRNA expression in epididymal WAT	Jeon et al. (2010), Maeda, Hosokawa, Sashima, Funayama, and Miyashita (2005), Maeda, Tsukui, Sashima, Hosokawa, and Miyashita (2008), Maeda, Hosokawa, Sashima, Murakami-Funayama, and Miyashita (2009)
Brown	*Undaria pinnatifida*	Japan	Fucoxanthin (acetone extract) (0.2% w/w)	KK-A(y) mice	↓ WAT weight gain ↑ UCP1 mRNA ↓ Leptin, TNF-α mRNA	Maeda et al. (2005), Maeda, Hosokawa, Sashima, and Miyashita (2007), Okada, Mizuno, Sibayama, Hosokawa, and Miyashita (2011)
Brown			Fucoidan (50, 100, and 200 μg/mL)	3T3-L1	↓ Lipid accumulation (ORO staining) ↓ C/EBP-α; PPAR-γ, aP2 mRNA ↓ p38 MAPKs, ERK, JNK activation factors	Kim, Lee, and Lee (2010)

Continued

Table 2 Summary of the effects of seaweed bioactives on adipose tissue.—cont'd

Seaweed color	Seaweed species	Country of origin	Extracts/specific compounds (concentration)	Biological model	Action	Reference source
Brown			Fucoidan (2% w/w)	Male C57BL/6 mice fed a high-fat diet	↓ Body-weight gain and epididymal fat mass ↓ PPAR-γ, aP2, ACC mRNA	Kim, Jeon, and Lee (2014), Kim, Rioux, and Turgeon (2014)
Red	*Gracilaria vermiculophylla papenfuss*	Korea	Ethanol extract/ethyl acetate fraction	3T3-L1	↓ Triglycerides accumulation (ORO staining) ↓ PPARγ, C/EBP-α, aP2 protein ↑ AMPK, LKB1 activation in mature adipocytes ↑ Intracellular ROS ↑ CPT1a, UCP2 mRNA	Kim et al. (2012)
Red	*Grateloupia lanceolata*	Korea	Ethanol extract (10 and 50 μg/mL)	3T3-L1	↓ Lipid accumulation (ORO staining) ↓ ROS production ↓ PPAR-γ and C/EBP-α mRNA, and aP2 protein ↓ Nox4, G6PDH mRNA ↑ SOD, glutathione peroxidase, catalase, adiponectin mRNA	Seo, Choi, Lee, and Lee (2013)
Red	*Plocamium telfairia*	South Korea	Ethanol extract (25, 50, 100 μg/mL)	3T3-L1	↓ Lipogenesis (ORO staining) ↓ PPAR-γ, C/EBP-α, SREBP1, FABP4 protein	Kang et al. (2016)

ACC, acyl-coA carboxylase; *aP2*, adipocytes protein 2; *C/EBP-α/β*, CCAAT/enhancer-binding proteins α/β; *CPT1a*, carnitine palmitoyltransferase-1a; *ERK*, extracellular signal-regulated kinases; *FA*, fatty acids; *FABP4*, fatty acid-binding protein 4; *FAS*, fatty acid synthase; *G6PDH*, NADPH-producing glucose-6-phosphate dehydrogenase; *JNK*, Jun N-terminal kinase; *IL-6*, interleukin-6; *LKB1*, liver kinase B1; *MCP-1*, monocyte chemoattractant protein-1; *Nox4*, nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase 4; *ORO*, oil red O; *PAI-1*, plasminogen activator inhibitor-1; *PPAR-γ*, peroxisome proliferator-activated receptor-γ; *ROS*, reactive oxygen species; *SOD*, superoxide dismutase; *SREBP-1c*, sterol regulatory element binding protein 1c; *UCP1*, uncoupling protein 1; *UCP2*, uncoupling protein 2; *TNFα*, tumor necrosis factor alpha; *WAT*, white adipose tissue.

macrocarpum (60.2%), *Polysiphonia morrowii* (55.0%), and *Ishige okamurae* (52.9%) had highest DPPH radical scavenging activities. Among the 49 species tested, extracts from *D. undulata, S. micracanthum, C. ocellatus, G. amansii, G. verrucosa*, and *G. lanceolate* (100 μg/mL) significantly decreased cellular fat accumulation, which was paralleled by inhibition of ROS production during the differentiation of 3T3-L1 preadipocytes (Lee, Yoon, Kim, You, & Lee, 2011). The ethanolic extract of *Caulerpa okamurae* (COE), at a concentration of 25–500 μg/mL, significantly inhibited lipid accumulation and reduced the expression of adipogenesis master regulators: C/EBP-α, PPAR-γ, and sterol regulatory element binding protein 1c (SREBP-1C) in 3T3-L1 adipocytes (Sharma et al., 2017). Extracts from *Ulva* spp., *Palmaria palmata, Undaria pinnatifida* and *Himanthalia elongata* at a concentration of 0.1 mg/mL were similarly shown to significantly inhibit triacylglycerol accumulation in mature 3T3-L1 adipocytes (43–52% inhibition) (Rico et al., 2018).

Extracts from red algae have also been studied for their anti-obesity properties. In particular, an ethanol extract from *Grateloupia lanceolata* (Okamura), a red seaweed native to coastal areas of East Asia, was shown to inhibit lipid accumulation (25% and 50% at 10 and 50 μg/mL concentrations, respectively) and ROS production (18% at 50 μg/mL) during adipogenesis in 3T3-L1 cells. Treatment with the *G. lanceolata* extract led to a reduction in the mRNA levels of the transcription factors PPAR-γ and C/EBP-α, and, at the protein level, for the target protein, fatty acid binding protein 2 (aP2). Moreover, ROS-producing nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase 4 (Nox4) and NADPH-producing glucose-6-phosphate dehydrogenase (G6PDH) mRNAs were decreased following *G. lanceolata* extract treatment, whereas mRNA levels of ROS scavenging enzymes, including superoxide dismutase (SOD), glutathione peroxidase, and catalase, were increased in the extract-treated group in addition to enhanced mRNA levels of adiponectin. These finding suggest that *G. lanceolata* extract inhibited lipid accumulation and ROS production by controlling adipogenic signals and ROS regulating genes (Seo et al., 2013). Similarly, an ethanol extract from the red seaweed *Plocamium telfairiae* (PTE) showed an inhibitory effect on lipogenesis in adipocytes (42.08%, 26.41%, and 17.86% at the concentrations of 25, 50, and 100 μg/mL, respectively) indicating that PTE reduced the accumulation of triglycerides in adipocytes. PTE treatment significantly decreased the expression (∼50%) of adipogenic-specific proteins such as PPAR-γ, C/EBP-α, SREBP1, and fatty acid binding protein 4 (FABP4) compared with untreated 3T3-L1 cells,

indicating that PTE inhibits adipogenic differentiation through down-regulation of adipogenic-specific proteins (Kang et al., 2016). In a different study, the ethyl acetate fraction of a komulkosiraegi (*Gracilaria vermiculophylla* (Ohmi) *Papenfuss*) ethanol extract (GEFr) was found to potently inhibit adipogenesis of 3T3-L1 preadipocytes, decreasing triglycerides accumulation and the expression of PPAR-γ, C/EPB-α, and aP2 at concentrations between 1 and 50 μg/mL. In mature adipocytes, GEFr was found to significantly activate AMP-activated protein kinase (AMPK) by activating liver kinase B1 (LKB1) and stimulating intracellular ROS. The mRNA levels of genes involved in lipid catabolism such as carnitine palmitoyltransferase-1a (CPT1a), and uncoupling protein 2 (UCP2) were also up-regulated (Kim et al., 2012).

2.2.2 Phlorotannins

The potential inhibitory effect of five species of brown seaweeds (*Sargassum thunbergii, Ishige okamurae, Ecklonia cava, Padina arborescens* and *Undaria wrightii*) on adipogenesis and differentiation of 3T3-L1 pre-adipocytes into mature adipocytes was assessed by Ko et al. (2013). The *Ecklonia cava* extract (100 μg/mL) showed profound adipogenesis inhibitory effect (40% reduction), compared to the other four brown seaweed extracts, and was then selected for isolation of active compounds including the three polyphenol compounds of phlorotannins, dieckol, 6,6′, bieckol and phlorofucofuroeckol A. Dieckol, at a concentration of 100 μM, exhibited greatest potential adipogenesis inhibition and down-regulated the expression of PPAR-γ, C/EBP-α, SREBP1 and fatty acid binding protein 4 (FABP4) in a dose-dependent manner by activating AMPK (Ko et al., 2013). The anti-obesity effects of 6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, dieckol and phlorofucofuroeckol A isolated from *Eisenia bicyclis* were also tested by Kwon et al. (2015), by examining the inhibition of differentiation of 3T3-L1 adipocytes and the expression of PPAR-γ, C/EBP-α and SREBP-1c at mRNA and protein level. Differentiated 3T3-L1 cells were treated with the purified phlorotannins at concentrations of 10, 25 and 50 μg/mL for 8 days. All the purified phlorotannins suppressed the differentiation of 3T3-L1 adipocytes in a dose-dependent manner, without toxic effects, however 6,6′-bieckol markedly decreased lipid accumulation and expression levels of PPAR-γ, C/EBP-α, SREBP-1c (mRNA and protein), and fatty acid synthase (FAS) and acyl-coA carboxylase (ACC) (mRNA), suggesting an effect of *E. bicyclis* through downregulation of adipogenesis and lipogenesis (Kwon et al., 2015).

Six indole derivatives (STCs)-indole-2-carboxaldehyde (STC-1), indole-3-carboxaldehyde (STC-2), indole-4-carboxaldehyde (STC-3), indole-5-carboxaldehyde (STC-4), indole-6-carboxaldehyde (STC-5), and indole-7-carboxaldehyde (STC-6) were extracted from *Sargassum thunbergii* and their inhibitory effects on adipocyte differentiation evaluated in 3T3-L1 cells at 25–100 μM. STC-1 and STC-5 resulted in non-toxic inhibition of 3T3-L1 adipocytes differentiation and significantly inhibited lipid accumulation and downregulated the protein expression of PPAR-γ, C/EBP-α, and SREBP-1c in a dose-dependent manner. The specific mechanism by which STC-1 and STC-5 inhibit lipid accumulation and adipogenesis in adipocytes involved AMPK activation and AMPK signaling pathway (Kang et al., 2017) Two bioactive subfractions from the brown alga *Fucus distichus*, a monoglycosyldiacylglycerol subfraction and a phlorotannin subfraction, decreased lipid accumulation up to 55% and increased free glycerol concentrations by 28–45% at a concentration of 50 μg/mL, paralleled by increases in adiponectin and uncoupling protein 1 (UCP-1) and decreases in leptin mRNA expression (Kellogg, Esposito, Grace, Komarnytsky, & Lila, 2015).

2.2.3 Complex polysaccharides

The sulfated polysaccharide fucoidan has been reported to affect the development of adipocytes, although its role in adipogenesis is not fully understood. Incubation of 3T3-L1 preadipocytes with 50, 100, and 200 μg/mL of fucoidan during differentiation induced a decrease in lipid accumulation of 29.1%, 50.5% and 52.4%, respectively. Furthermore, 200 μg/mL fucoidan induced down regulation in gene expression of both early (22% reduction for C/EBP-α and 17.6% for PPAR-γ) and late (73.9% reduction for activating protein 2 (aP2)) adipogenic markers, which have a crucial role in adipocyte development. Early activation of p38 MAPKs, extracellular signal-regulated kinases (ERK) and Jun N-terminal kinase (JNK) was also inhibited by fucoidan suggesting a potential role of fucoidan in inhibiting adipogenesis in 3T3-L1 preadipocytes, by affecting the MAPK signaling pathway that involves adipogenic transcription factors (Kim et al., 2010). Similarly, fucoidan extracted from the sporophyll of *U. pinnatifida* (100 μg/mL) exerted anti-obesity effects via suppressing the expression of PPAR-γ (36%), C/EBP-α (44%), and aP2 (71%), which decreased expression of the inflammation-related genes such as tumor necrosis factor alpha (TNFα, 35%), monocyte chemoattractant protein-1 (MCP-1, 66%) and plasminogen activator inhibitor-1 (PAI-1, 29%) during adipogenesis.

Moreover, fucoidan reduced lipid accumulation and ROS production in adipocytes, demonstrating that fucoidan from the sporophyll of *U. pinnatifida* may suppress adipogenesis through inhibition of major adipogenesis markers and inflammation-related cytokines in adipocytes (Kim & Lee, 2012). Four fucoidan-rich fractions (F0.5, F0.9, F1.1 and F2.0) obtained by differential precipitation with acetone from a commercial source of fucoidan from *Fucus vesiculosus* and containing different proportions of fucose:glucuronic acid:galactose:xylose:sulfate, were tested in 3T3-L1 cells for their lipolytic and anti-adipogenic activity at a concentration of 200 μg/mL. All samples had lipolytic action, especially F2.0, which tripled the amount of glycerol released in the cellular medium, whereas antiadipogenic activity was limited to F1.1 and F2.0 with F0.5 inducing adipogenesis, as determined by oil red O staining. The effect of the different fractions on adipogenesis was matched by the expression of key proteins of adipogenic differentiation (C/EBP-α, C/EBP-β, and PPAR-γ) with F2.0 decreasing their levels by 55%. Not all the fractions had similar effects, suggesting that the relative amount of fucose:glucuronic acid:galactose:xylose:sulfate affects differently their potential as anti-obesity compounds (Oliveira et al., 2018).

2.2.4 Carotenoids—Fucoxanthin

Fucoxanthin (Fx) is a marine carotenoid found in edible brown seaweeds and has been associated with lipid metabolism. Fx isolated from *Sargassum echinocarpum* was added to pre-adipocyte cell obtained from viscera tissue of Wistar rats and was able to increase adiponectin levels and decrease of TNF-α expression suggesting its ability to enhance β-oxidation in adipocyte cells (Firdaus et al., 2015). In differentiating 3T3-F442A adipocytes, fucoxanthinol, which is a fucoxanthin metabolite found in white adipose tissue (WAT), attenuated TNF-α-induced monocyte chemotactic protein-1 (MCP-1) and interleukin-6 (IL-6) mRNA overexpression and protein secretion into the culture medium. In addition, fucoxanthinol decreased TNF-α, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) mRNA expression in RAW264.7 macrophage-like cells stimulated by palmitic acid (Hosokawa et al., 2010).

2.2.5 Animal studies

Some of the molecular mechanisms identified to be affected by seaweed extracts or bioactive compounds treatment in cell models of obesity have also been the focus of studies in adipose tissue from animal model of obesity. For example, supplementation of a high-fat diet with an ethanol extract of

Caulerpa okamurae (COE) (250 m/kg) significantly reduced PPAR-γ, C/EBP-α, FAS, SRBP1c, cluster of differentiation 36, and acetyl-CoA synthetase in the adipose tissue of COE-treated HFD-fed mice in addition to a reduction in markers of weight gain. These included free fatty acids, triglycerides, total cholesterol, glucose and insulin in the plasma and free fatty acids, triglycerides, total cholesterol and total lipid in the liver (Sharma et al., 2017). Fucoidan (2%) administered to mice fed either a standard diet or high fat diet (HFD) for 5 weeks significantly decreased body-weight gain (47.3%), food efficiency ratio and relative liver and epididymal fat mass (16.1% and 32% reduction, respectively), compared with the HFD group. Furthermore, fucoidan affected adipogenesis in epididymal adipose tissue, by decreasing the expression of adipogenic genes, such as PPAR-γ, aP2 and ACC by 34.0%, 36.4% and 28.4%, respectively, in the 2% supplemented group compared with the HFD group (Kim, Jeon, & Lee, 2014).

Fucoxanthin (Fx), extracted from the commercial *Undaria pinnatifida* seaweed powder using acetone and further purified by silica gel column chromatography with n-hexane/acetone (8:2, v/v), was administered to diabetic/obese KK-A(y) mice as part of their diet (0.2% Fx), and attenuated WAT weight gain and hyperglycemia, although it did not affect these parameters in lean C57BL/6J mice. In perigonadal and mesenteric WAT of KK-A(y) mice fed Fx, mRNA expression levels of MCP-1 and TNF-α were markedly reduced compared to control mice. In contrast to KK-A(y) mice, Fx did not alter MCP-1 and TNF-α mRNA expression levels in the WAT of lean C57BL/6J mice. Moreover interleukin-6 (IL-6) and PAI-1 mRNA expression levels in WAT were also decreased by Fx in KK-A(y) mice, suggesting that Fx regulates mRNA expression of inflammatory adipocytokines in WAT and has specific effects on diabetic/obese KK-A(y) mice (Hosokawa et al., 2010). Similar findings were obtained by Maeda et al. (2007) in a study that evaluated the anti-obesity and antidiabetic effects of Fx (0.2%, obtained from commercial *Undaria pinnatifida* dried seaweed after acetone extraction and purification by silica gel column chromatography with n-hexane/acetone (7:3, v/v)) in KK-A(y) mice. After 4 weeks of feeding, 0.2% Fx in the diet markedly attenuated the gain of WAT weight in KK-A(y) mice with increasing UCP1 expression compared with the control mice. Leptin and TNF-α mRNA expression in WAT were significantly down-regulated by 0.2% Fx, suggesting that Fx might influence inflammation and energy metabolism (Maeda et al., 2007). An additional study by Jeon et al. (2010) examined the effectiveness of an ethanol extract of Fx-rich seaweed as a nutraceutical for body fat-lowering agent and for an anti-obesity effect based on mode of actions in

C57BL/6J mice. Animals were randomized to receive a semi-purified high fat diet supplemented with 0.2% conjugated linoleic acid (CLA) as positive control, and 1.43% or 5.72% Fx-rich seaweed ethanol extract (Fx-SEE), equivalent to 0.05% or 0.2% dietary Fx for 6 weeks. Fx-SEE significantly reduced body and abdominal WAT weights, plasma and hepatic triglyceride (TG), and/or cholesterol concentrations compared to the high fat control group. Activities of adipocytic fatty acid (FA) synthesis, hepatic FA and TG synthesis, and cholesterol-regulating enzyme were also lowered by Fx-SEE supplement. Concentrations of plasma HDL-cholesterol, fecal TG and cholesterol, as well as FA oxidation enzyme activity and UCP1 mRNA expression in epididymal WAT were significantly higher in the Fx-SEE groups than in the high fat control group, indicating that Fx-SEE affects the plasma and hepatic lipid profile, fecal lipids and body fat mass, and alters hepatic cholesterol metabolism, FA synthesis and lipid absorption (Jeon et al., 2010). Several other studies have focused their attention on the effect of Fx rich extracts on UCP1 expression: a key molecule for metabolic thermogenesis to avoid fat accumulation excess is usually expressed only in brown adipose tissue (BAT), and, therefore, its expression in tissues other than BAT is expected to reduce abdominal fat. Fx rich lipid fractions from *Undaria pinnatifida* (Maeda et al., 2005, 2008, 2009; Okada et al., 2011) fed to mice in addition to a high-fat diet significantly suppressed body weight and WAT weight gain induced by the HF diet by upregulating the expression of UCP1 in WAT, which may contribute to reducing WAT weight and ameliorate alterations in lipid metabolism.

The above studies provide a good starting point to identify therapeutic targets that link metabolic disorders with altered adipocyte function. Adipocyte hyperplasia and hypertrophy are key processes in metabolic dysfunction; a "critical" adipocyte size exists that triggers the recruitment of preadipocytes that will differentiate into mature adipocytes and induce changes in levels of ROS and inflammatory molecules and their subsequent deleterious effects at cellular/tissue level. Targeting some of the key proteins involved in such tightly regulated processes or adipocyte-derived secretory proteins and their receptors with seaweed extracts and bioactive compounds may, therefore, provide promising pharmacological targets.

2.3 Activity of seaweed extracts and bioactive compounds in liver

The liver has long been recognized to be an essential metabolic organ and plays a crucial role in whole-body energy homeostasis by regulating the

metabolism of nutrients. When carbohydrates are abundant, during the postprandial phase, the liver converts glucose into glycogen and lipids, which provide metabolic fuels during fasting. In the fasted state, the liver produces and secretes glucose through both glycogenolysis and gluconeogenesis. The metabolic switch between fasted and fed states in the liver is tightly controlled by neuronal and hormonal systems and, in obesity, such switches are affected: adipose tissue regulates liver energy metabolism directly by secreting a variety of adipokines including adiponectin and cytokines, and, indirectly, by secreting leptin which acts on the brain to regulate liver metabolism. The liver also regulates the metabolic activity of adipose tissue. Bioactive compounds that affect liver energy metabolism may have beneficial effects as potential anti-obesity drugs: examples of the effect of seaweed extracts or their bioactive compounds are reported below, and the findings summarized in Table 3.

2.3.1 Whole seaweed and seaweed extracts

Studies have assessed the effect of feeding a diet containing the brown seaweed *Undaria pinnatifida* (wakame) (0, 0.1, or 1.0 g/100 g diet of dried wakame powder) to rats for 28 days. Administration of 1% wakame significantly decreased serum total cholesterol levels, and in the liver suppressed the lipogenic pathway by downregulating SREBF-1. Moreover, gluconeogenesis was promoted by upregulation of the PPAR signaling pathway, which leads to a reduction in the accumulation of cholesterol and promotion of β-oxidation, suggesting that wakame ingestion affects glucose and lipid metabolism by altering the expression of SREBP-1 and PPAR signal-related genes (Yoshinaga et al., 2018).

2.3.2 Carotenoids—Fucoxanthin

The effect of Fx on hepatic stearoyl-coenzyme A desaturase-1 (SCD1), a rate-limiting enzyme that catalyzes the biosynthesis of monounsaturated fatty acids from saturated fatty acids, has been studied in obese mouse models of hyperleptinemia (KK-A(y)) and leptin-deficiency (ob/ob). In KK-A(y) mice fed a diet containing 0.2% Fx for 2 weeks, SCD1 mRNA and protein expression were reduced in the liver with a concomitant decrease in serum leptin levels. In contrast, the suppressive effects of Fx on hepatic SCD1 and body weight gain were not observed in leptin-deficient ob/ob mice. These findings support the hypothesis that Fx down-regulates SCD1 expression and alters fatty acid composition of the liver through regulation of leptin signaling (Beppu et al., 2013).

Table 3 Summary of the metabolic effects of seaweed extracts on the liver.

Seaweed color	Seaweed species	Country of origin	Extracts/specific compounds (concentration)	Biological model	Action	Reference source
Liver						
Brown	*Phaeodactylum tricornutum*		Fucoxanthin (acetone extract) (0.2% w/w)	Male C57BL/6J mice fed high-fat diet	↑ SOD, catalase, glutathione peroxidase activity ↓ TBARS, glutathione levels	Kang, Kim, et al. (2013), Kang, Wijesinghe, et al. (2013)
Brown	*Undaria pinnatifida*	Japan	Dried seaweed (0.1, 1.0 g/100 g diet)	Male Sprague-Dawley fed high-fat diet	↓ Lipogenic pathway by downregulating SREBF-1 ↑ Gluconeogenesis ↑ PPAR signaling pathway	Yoshinaga, Maruya, Koikeda, and Nakano (2018)
Brown	*Undaria pinnatifida*	Japan	Fucoxanthin (acetone extract) (0.2% w/w)	KK-A(y) and ob/ob mice	↓ SCD1 mRNA and protein in KK-A(y) not in ob/ob	Beppu, Hosokawa, Yim, Shinoda, and Miyashita (2013)
Brown			Fucoxanthin (0.2% w/w)	Male Sprague-Dawley fed high-fat diet	↑ Catalase and GSH-Px activity ↑ Nrf2, NQO1 mRNA	Ha, Na, and Kim (2013)

GSH-Px, glutathione peroxidase; *Nrf2*, nuclear erythroid factor like 2; *NQO1*, NAD(P)H quinone oxidoreductase1 (NQO1); *PPAR-γ*, peroxisome proliferator-activated receptor-γ; *SCD1*, stearoyl-coenzyme A desaturase; *SOD*, superoxide dismutase; *SREBP-1c*, sterol regulatory element binding protein 1c; *TBARS*, thiobarbituric acid reactive substances.

An alternative mechanism by which Fx may act as an anti-obesity compound is through modulation of liver antioxidant capacity to reduce intracellular ROS levels, which have been shown to mediate adipocyte differentiation (Kanda, Hinata, Kang, & Watanabe, 2011). Although not a seaweed, co-administration of the Fx-containing diatom *Phaeodactylum tricornutum* (0.7% lipid extract corresponding to 0.2% Fx) with a high-fat diet to mice for 8 weeks increased hepatic superoxide dismutase, catalase, and glutathione peroxidase activities and decreased thiobarbituric acid reactive substances (TBARS) and glutathione levels. Moreover, body weight and epididymal WAT was significantly decreased compared to mice fed the high-fat diet. Serum triglyceride, glucose, insulin, and leptin levels were also significantly lower in the *P. tricornutum* group than in the high-fat diet group (Kang, Kim, et al., 2013). Similar results were obtained in a different study: liver activities of catalase and GSH-Px were significantly higher in the high-fat diet + Fx group than those in the high-fat diet group and were increased by Fx by inducing higher mRNA expression of transcription factor, nuclear erythroid factor like 2 (Nrf2), and its target genes such as NAD(P)H quinone oxidoreductase1 (NQO1), suggesting that Fx supplementation improved liver antioxidant capacity, depleted by high-fat diet, by activating the Nrf2 pathway (Ha et al., 2013).

2.4 Activity of seaweed extracts and bioactive compounds on the gut microbiota

It is now recognized that modulating the diversity of gut microbiota, through dietary intervention, may significantly affect gut health as well as systemic health. Recent studies have implicated the gut microbiota as a critical determinant of nutrient uptake, energy regulation, and chronic metabolic disorders (Moreno-Indias, Cardona, Tinahones, & Queipo-Ortuno, 2014). The human gut contains a vast number and diversity of microorganisms that are shaped by natural selection and competition. Bioactive compounds able to modify the composition of the gut microbiota are gathering interest as changes they induced could improve nutrient utilization and increase microbial metabolite production, thus regulating lipid uptake and metabolism in the body in the case of obesity. Some of the very few studies that have looked at changes in gut microflora induced by seaweeds and/or their bioactive compounds are reported below and findings summarized in Table 4.

Table 4 Summary of the effects of seaweed extracts on the gut microbiota.

Seaweed color	Seaweed species	Country of origin	Extracts/specific compounds (concentration)	Biological model	Action	Reference source
Intestine—gut microflora						
Brown	*Ascophyllum nodosum Laminaria japonica*	China	Fucoidan (200 mg/kg)	Male C57BL/6 mice fed high-fat diet	↓ Body weight, fasting blood glucose, hepatic steatosis and systematic inflammation ↑ Benign microbes—*Akkermansia muciniphila* ↑ Short-chain fatty acid-producers—*Alloprevotella, Blautia, Bacteroides*	Shang et al. (2017)
Brown	*Laminaria japonica*	South Korea	Dried whole seaweed or heat treated dried whole seaweed (10% w/w)	Male Sprague-Dawley rats	↓ Body weight gain ↓ *Fimicutes* to *Bacteroidetes* ratio ↓ Obesity-associated bacterial genera—*Allobaculum, Turicibacter, Coprobacillus, Mollicute, Oscilibacter* ↓ Potential pathogenic genera—*Mollicute, Bacteroides, Clostridium, Escherichia, Prevotella* ↑ Leanness-associated genera—*Alistipes, Bacteroides*, and *Prevotella* ↑ Lactic acid bacterial genera—*Subdoligranulum, Streptococcus, Lactobacillus, Enterococcus, Bifidobacterium*	Kim et al. (2018)

Brown	*Laminaria japonica*	China	Alginates (pressurized hot water extraction) (0.25% w/w)	Male BALB/c mice fed high-fat diet	↓ Body weight, fat accumulation in liver and WAT = species richness of the gut microbiota ↑ *Rikenellaceae* and *Bacteroidales S24_7* = *Prevotellaceae* family	Duan et al. (2019)
Red Green	*Porphyra haitanensis* *Ulva prolifera*	China	Polysaccharides (hot water extraction) (250 mg/kg per day)	Male C57BL/6 mice	↑ *Bacteroidetes* contributing to fecal microbiota ↓ *Firmicutes* ↑ *Prevotellaceae UCG-001*, *Rikenellaceae RC9*	Zhang et al. (2018)
Brown	*Undaria pinnatifida*	Japan	Dried whole seaweed (4 g of dried wakame per day)	Healthy individuals suffering from low defecation frequency	↑ Defecation frequency and volume per week ↑ *Bifidobacteria* as a percentage of all fecal bacteria ↑ *Actinobacteria* relative abundance ↓ *Bacteroidetes* abundance	Yoshinaga et al. (2018)
Brown			Polymannuric acid (150 mg/kg body weight/day)	Male C57BL/6 mice fed high-fat diet	↓ Body weight gain ↑ Probiotic bacterium *Lactobacillus reuteri*	Liu et al. (2017)
Red	*Kappaphycus alvarezii*	Fiji	Dried whole seaweed (5% w/w)	Male Wistar rats fed a high/carbohydrate, high-fat diet	↓ Body weight and abdominal fat ↓ *Firmicutes* to *Bacteroidetes* ratio	Wanyonyi et al. (2017)

2.4.1 Whole seaweed and seaweed extracts

The prebiotic potential of the brown seaweed *Laminaria japonica* was tested by feeding a basal diet (control), basal diet supplemented with dried *L. japonica* (DLJ) or heat-treated dried *L. japonica* (HLJ), to rats for 16 weeks. The DLJ and HLJ groups had lower weight gain and serum triglyceride concentration compared to the control group and showed lower *Fimicutes* to *Bacteroidetes* ratio when compared with the control group. Moreover, obesity-associated bacterial genera (*Allobaculum, Turicibacter, Coprobacillus, Mollicute*, and *Oscilibacter*), and the genera with pathogenic potentials (*Mollicute, Bacteroides, Clostridium, Escherichia*, and *Prevotella*) decreased while leanness-associated genera (*Alistipes, Bacteroides*, and *Prevotella*), and lactic acid bacterial genera (*Subdoligranulum, Streptococcus, Lactobacillus, Enterococcus*, and *Bifidobacterium*) increased in all treatment groups, pointing to the potential of *L. japonica* as an effective prebiotic for promotion of host metabolism and reduction of obesity in humans (Kim et al., 2018). Relative to obese rats, animals treated with the red seaweed, *Kappaphycus alvarezii* (5% (w/w) dried and milled Kappaphycus) showed normalized body weight and adiposity, lower systolic blood pressure, improved heart and liver structure, and lower plasma lipids, even in presence of high-fat diet. *Kappaphycus* modulated the balance between *Firmicutes* and *Bacteroidetes* in the gut, which could serve as the potential mechanism for improved metabolic variables and was accompanied by no damage to the gut structure (Wanyonyi, Du Preez, Brown, Paul, & Panchal, 2017).

The ability of bioactive compounds from seaweed to affect gut microflora has also been tested in humans. The effect of a 2-week intake of the edible seaweed *Undaria pinnatifida* (wakame) on defecation frequency and intestinal microbiota was tested in 22 healthy individuals suffering from low defecation frequency. Supplementation of their diet with wakame significantly increased defecation frequency and volume per week in addition to increasing the fraction of *Bifidobacteria* as a percentage of all fecal bacteria and the relative abundance of *Actinobacteria*, while the abundance of *Bacteroidetes* decreased (Yoshinaga et al., 2018).

2.4.2 Polysaccharides

Polysaccharides from *Laminaria japonica* (LJPs) also prevented diet-induced obesity in a murine model, and improved obesity-related parameters (e.g., fat accumulation in the liver and adipose tissues, body composition, lipid profile) as well as the morphology of the intestine: such effects were

associated with the modulation of the gut microbiota, involving some members of the *Bacteroidetes* phylum (Duan et al., 2019). Polysaccharides from two seaweeds, *Porphyra haitanensis* (PH) and *Ulva prolifera* (UP), also affected the intestinal microbiota in mice gavaged with 250 mg/kg per day: significant structural changes in the fecal microbiota were observed between the two treated groups and the control group, with changes evident at the phylum and genus levels. At the phylum level, the most predominant phylum was *Bacteroidetes* contributing 58.76%, 73.39% and 75.38% of the fecal microbiota in the control, PH and UP groups, respectively, followed by *Firmicutes*, contributing 37.61%, 23.99% and 21.87%. Many genera were significantly higher in the PH and UP group than in the control group, including *Prevotellaceae UCG-001* and *Rikenellaceae RC9* (Zhang, Wang, Han, Liu, & Liu, 2018). Similarly a 30-day treatment with polymannuric acid (PM), one of numerous alginates isolated from brown seaweeds, in mice fed a high-fat diet-induced a reduction in body weight gain and blood TAG levels (P2.0), but also had a profound impact on the microbial composition in the gut microbiome and resulted in a distinct microbiome structure and increased the abundance of a probiotic bacterium, *Lactobacillus reuteri* ($\log_{10}$ LDA score >2.0) (Liu et al., 2017). Two fucoidans from *Laminaria japonica* and *Ascophyllum nodosum* were also tested and found to significantly reduce body weight, fasting blood glucose, hepatic steatosis and systematic inflammation. As fucoidan is poorly absorbed after oral administration, in order to decipher the mechanism behind this therapeutic effect, the gut microbiota was analyzed: benign microbes, which conferred benefits upon host wellbeing including *Akkermansia muciniphila* and short-chain fatty acid-producers such as *Alloprevotella, Blautia* and *Bacteroides* were highly enriched by fucoidans (Shang et al., 2017).

2.5 Summary of the metabolic effects of seaweed in obesity

Obesity and overweight processes are determined not only by adipocyte hyperplasia and adipose tissues hypertrophy, but also by changes in liver energy metabolism and gut microbiota as a critical determinant of nutrients uptake and energy regulation. Pharmacological interventions focused on maintaining or improving adipose tissue health and liver energy metabolism, and modulating the diversity of gut microbiota, therefore forms the basis for therapeutic interventions in metabolic diseases. As described in the above sections, extracts from seaweeds and their bioactive compounds provide a good resource for discovering new therapeutic drugs for obesity management.

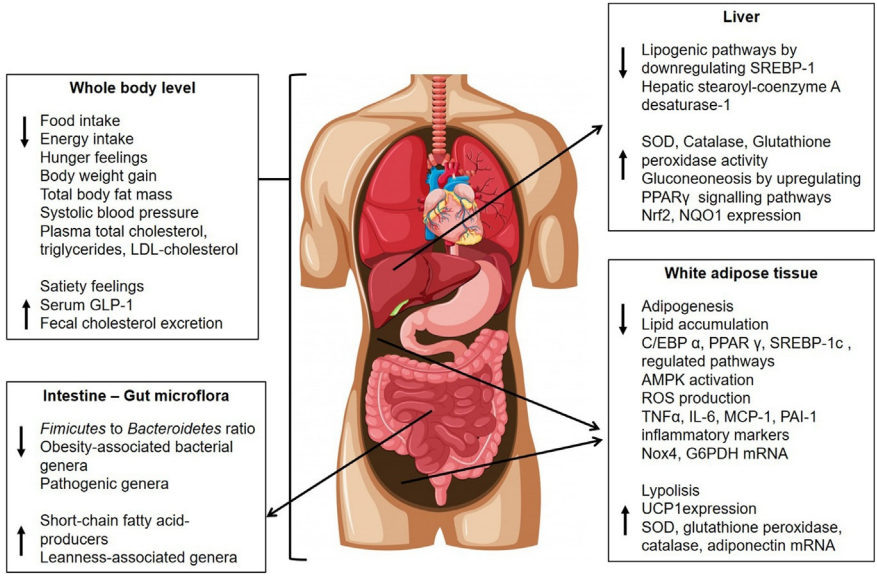

Fig. 1 Diagram summarizing the effects of seaweed extracts and bioactive compounds at whole body level, and on the adipose tissue, liver and gut microflora.

The molecular mechanisms affected by seaweed extracts and bioactive compounds are specific to different tissues (Fig. 1); however modulation of antioxidant capacity and reduction of intracellular ROS levels within tissues are the key mechanisms identified. At adipose tissue level, the programmed differentiation of preadipocytes into mature adipocytes is characterized by chronological changes in the expression of numerous genes and proteins, such as PPAR-γ, C/EBP family, SREBP-1c, and aP2, and is mediated by intracellular ROS levels. Seaweed extracts reduce the expression of Nox4 and G6PDH with subsequent increased activation of ROS scavenging enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase. Moreover, modulation of adipogenesis also occurs via regulation of inflammation-related cytokines such as TNFα, MCP-1 and PAI-1: seaweed extracts affect such pathways in addition to induce the expression of the metabolic thermogenesis regulator UCP1. Similarly, in the liver suppression of lipogenic pathways and upregulation of gluconeogenesis and promotion of β-oxidation have been induced by seaweed extracts in addition to increasing activities of superoxide dismutase, catalase, and glutathione peroxidase by activating the Nrf2 pathway and improving liver antioxidant capacity.

Future studies aimed at discovering new therapeutic drugs from marine natural products should, therefore, focus on bioactive compounds from

seaweeds that exert antioxidant properties and regulate the expression of key signaling pathways involved in enhancing browning of white adipose tissue, and reducing oxidative stress in adipose tissue and liver.

3. Metabolic effects of seaweed in type 2 diabetes

The main pharmacological approaches for the management of T2D involve the use of agents that target key events, from the point of entry of glucose into the circulation to the responsiveness to insulin at the cellular level (Fig. 2). For example, consumed dietary saccharides are hydrolyzed to absorbable glucose by the enzymes α-glucosidase and α-amylase in the gastrointestinal brush border, and so inhibitors of α-glucosidase (e.g., acarbose) are used to reduce the absorption and/or digestion of dietary saccharides to diminish post-prandial blood glucose. Glucagon-like peptide-1 (GLP-1), is released in response to ingestion of food and stimulates the release of insulin from pancreatic β-cells and GLP-1 agonists (e.g., exenatide) are used to mimic GLP-1, while inhibitors of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for the breakdown of GLP-1, are used to prolong its half-life (e.g., linagliptin), while the second generation sulfonylureas (e.g., glibenclamide) are used to directly stimulate pancreatic insulin secretion. At the cellular level, the metabolic actions of insulin can be enhanced by the biguanides (e.g., metformin) or the thiazolidinedione (e.g., pioglitazone)

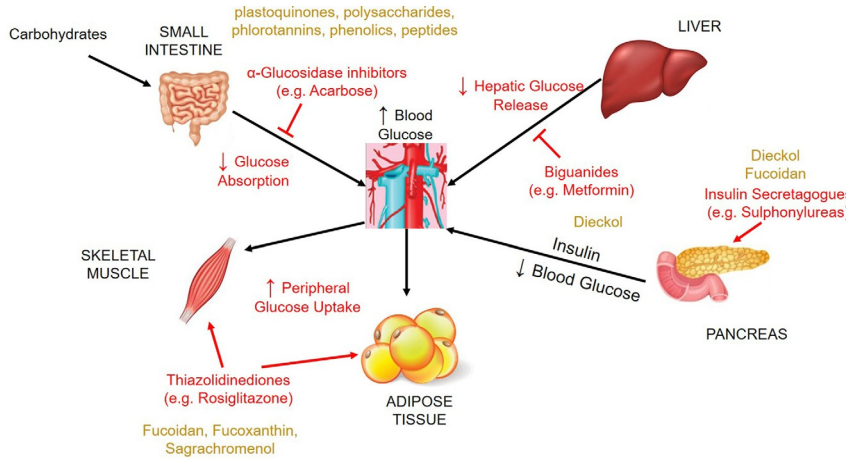

Fig. 2 Diagram illustrating sites of action of anti-diabetic drugs used in the management of T2D (red) and possible sites of action of bioactive molecules from seaweed (brown).

insulin sensitizers, the latter acting through PPAR-γ activation. Most of the studies to date into the anti-diabetic potential of seaweed/algae-based extracts, and pure compounds derived from them, have therefore focused on some of these pharmacological targets, but have also assessed their effectiveness at other potential targets.

3.1 α-Glucosidase and α-amylase inhibitory activity of algal extracts

Hyperglycemia can be suppressed using drugs that delay or prevent the absorption of glucose from the intestine, and the key digestive enzymes α-glucosidase and α-amylase, which are responsible for the breakdown of starch into glucose, represent an ideal target. The main clinically utilized drug to achieve this is acarbose, which inhibits both enzymes, however there are significant adverse effects associated with its use (abdominal discomfort, diarrhea and flatulence) that are believed to be due to inhibition of pancreatic amylase. Therefore, the optimum approach would be to inhibit α-glucosidase alone, and it is selective inhibition of this enzyme that has been the main focus for the exploration of the anti-diabetic potential of seaweed (Table 5).

3.1.1 In vitro studies

Most studies have focused on brown seaweed species, of which the *Ascophyllum nodosum* species is probably the most widely studied, and one of the very first reports found that oral administration of a polyphenol-enriched extract of *A. nodosum* to streptozotocin diabetic mice resulted in a modest improvement in fasting glucose alongside a blunted increase in blood glucose following oral sucrose tolerance testing, while in vitro studies (rat intestinal α-glucosidase) provided direct evidence of the ability of the extract to inhibit the enzyme (Zhang et al., 2007). Subsequent studies revealed that while a phenolic-rich extract of *A. nodosum* inhibits both α-glucosidase and α-amylase, it is a more potent inhibitor of α-glucosidase than acarbose and its IC_{50} for α-amylase inhibition is greater than that of acarbose, suggesting preference for α-glucosidase over α-amylase inhibition (Apostolidis & Lee, 2010). The importance of phenolic content in the ability of *A. nodosum* extract to inhibit α-glucosidase has been confirmed by studies on extracts of the seaweed harvested at different times of the year from the north eastern coastal waters of the United Sates, where seasonal variations in phenolic content (lowest in April and highest in July) revealed an inverse relationship between IC_{70} values for enzyme inhibition and total phenolic

Table 5 Summary of the α-glucosidase and α-amylase inhibitory effects of seaweed bioactives.

			α-Glucosidase inhibition (IC_{50})		α-Amylase inhibition (IC_{50})		
Seaweed species	**Country of origin**	**Chemicals present**	**Extract/ compound**	**Acarbose**	**Extract/ compound**	**Acarbose**	**Reference source**
Ascophyllum nodosum	Japan	Polyphenol-enriched	77 μg/mL	–	ND	–	Zhang et al. (2007)
	USA	Phenolic 4.2 mg/g ww	0.24 μg	0.37 μg	1.34 μg	0.68 μg	Apostolidis and Lee (2010)
	Ireland	Phenolic 44–56 (GAE/mg)	<1 μg/mL	150 μg/mL	44–53 μg/mL	ND	Lordan, Smyth, Soler-Vila, Stanton, and Ross (2013)
	Scotland	Phenolic 140–4550 (μg/gDW)	19 μg/mL	ND	0.1 μg/mL	ND	Nwosu et al. (2011)
	Scotland	Phenolic—171–363 μg GAE/mL Phlorotannin	10 μg GAE/mL 10 μg GAE/mL	40 μg/mL	0.05 μg GAE/mL 0.15 μg GAE/mL	1 μg/mL	Pantidos, Boath, Lund, Conner, and McDougall (2014)
	Canada	Fucoidan	13–47 μg/mL	1 mg/mL	0.12–4.64 mg/mL	1 mg/mL	Kim, Rioux, and Turgeon (2014)
Ecklonia cava	Korea	Dieckol	0.24 mM	1.05 mM	0.66 mM	1.09 mM	Lee et al. (2010)
Fucus distichus	USA	Phlorotannins comprising 3–18 fucophloroethol monomers	0.89 μg/mL	112 μg/mL	13.9 μg/mL	137.8 μg/mL	Kellogg, Grace, and Lila (2014)
Fucus vesiculosis	Canada China	Fucoidan Fucoidan	49 μg/mL 68 μg/mL	1 mg/mL ND	>10 mg/mL >10 mg/mL	1 mg/mL ND	Kim, Jeon, and Lee (2014), Kim, Rioux, and Turgeon (2014)

Continued

Table 5 Summary of the α-glucosidase and α-amylase inhibitory effects of seaweed bioactives.—cont'd

			α-Glucosidase inhibition (IC_{50})		α-Amylase inhibition (IC_{50})		
Seaweed species	**Country of origin**	**Chemicals present**	**Extract/ compound**	**Acarbose**	**Extract/ compound**	**Acarbose**	**Reference source**
Ascophyllum nodosum and *Fucus vesiculosis*	Italy	Polysaccharides, polyphenols, fatty acids	1.5 μg/mL	130 μg/mL	0.6 μg/mL	207 μg/mL	Gabbia et al. (2017)
Hizikia fusiformis	South Korea	Fucoxanthin, fucosterol	40–60 μg/mL	231 μg/mL	ND	ND	Han, Ali, Woo, Jung, and Choi (2015)
Ishige okamurae	South Korea	Diphlorethohydroxycarmolol (DPHC)	0.16 mM	1.05 mM	0.53 mM	1.10 mM	Heo et al. (2009)
Laminaria digitata	Germany	Extract 2,5-dihydrobenzoic acid	750 μg/mL 46 μg/mL	1120 μg/mL	ND	ND	Zaharudin, Salmean, and Dragsted (2018)
Laminaria japonica	China	Polysaccharides	7500 μg/mL	ND	58 mg/mL	ND	Peng, Yuan, Wu, and Wang (2011)
Sargassum confusum	China	Polysaccharide hydrolysate (SCO)	9.9 mg/mL	3.0 mg/mL	ND	ND	Yang et al. (2017)
Sargassum hemiphyllum	Taiwan	Polyphenols 17–36 mg/g Fucoxanthin 8–15 mg/g	ND	ND	350 μg/mL	0.7 μg/mL	Hwang, Hung, Tsai, Chien, and Kong (2015)
Sargassum serratifolium	Korea	Sargachromenol Sargaquinoic acid	43 μM 96 μM	210 μM	ND	ND	Ali et al. (2017)

Sargassum wightii	India	Fucoidan	132 μg/mL	1 mg/mL	ND	ND	Kumar et al. (2015)
Turbinara conoides	India	Fucoidan	0.68 μM	3.5 μM	1.07 μM	5.3 μM	Lakshmana Senthil, Raghu, Arjun, and Anantharaman (2019)
Turbinaria ornata	India	Fucoidan	ND	ND	33.6 μg/mL	125 μg/mL	Lakshmana Senthil et al. (2014)
Undaria pinnatifida	N/K	Fucoxanthin	47 μg/mL	600 μg/mL	ND	ND	Zaharudin, Staerk, and Dragsted (2019)
Eucheuma denticulatum	Malaysia	Not determined, but known to contain polyphenols	ND	ND	67% Inhibition at 10 mg/mL	92% Inhibition at 1 mg/mL	Balasubramaniam et al. (2016)
Porphyra spp.	China	Gly-Gly-Ser-Lys Glu-Leu-Ser	ND ND ND	ND	1.86 mg/mL 2.6 mM 2.6 mM	ND	Admassu, Gasmalla, Yang, and Zhao (2018)
Halimeda macroloba	Malaysia	Not determined, but extracts in water	6.4 mg/mL	<1 mg/mL	ND	ND	Chin et al. (2015)
Codum fragile	Tunisia	Sulfated polysaccharides	ND	ND	~50% inhibition in vivo following 150 mg/kg p.o.	~50% inhibition following 5 mg/kg p.o.	Kolsi, Fakhfakh, Sassi, Elleuch, and Gargouri (2018)
Ulva fasciata	Malaysia	Terpenoids, flavonoids, glycosides and phenolics	ND	ND	69 μg/mL	49 μg/mL	Mohapatra, Bhattamisra, Panigrahy, and Parida (2018)

content (Apostolidis, Karayannakidis, Kwon, Lee, & Seeram, 2011). Other studies using both water- and ethanol-based extracts from *A. nodosum* have similarly shown a preference for α-glucosidase inhibition over α-amylase inhibition (Lordan et al., 2013) and superiority over acarbose at inhibiting α-glucosidase. In contrast, other studies have shown that the α-amylase inhibitory activity of *A. nodosum* extracts is greater than the α-glucosidase inhibitory activity (Nwosu et al., 2011), differences that can potentially be explained by variances in the extraction process. For example, the Sephadex fractionation process employed by Nwosu et al. (2011) resulted in a phenolic-rich fraction, while the water-based extraction employed by the Apostolidis group (Apostolidis et al., 2011) may have contained a greater amount of non-phenolic components that may have contributed to the greater inhibition of α-glucosidase. Subsequent comparison of the inhibitory activity of phenolic-enriched and phlorotannin-rich sub fractions of *A. nodosum* revealed that only the phenolic-enriched, but not the phlorotannin-rich, fractions exhibited α-amylase inhibitory activity, while both fractions inhibited α-glucosidase equally; interestingly, the presence of bovine serum albumin attenuated the inhibitory activity of the phlorotannin-rich fraction against α-amylase, suggestive of protein binding playing an important part in its mechanism of action (Pantidos et al., 2014). Moreover, co-incubation of the phlorotannin-rich fraction along with acarbose reduced the concentration of acarbose required to inhibit both enzymes, leading to the suggestion that a combination of acarbose with phlorotannin-rich seaweed extracts may be a suitable approach to the management of post-prandial glycemic control.

Findings from other brown seaweed species have found that α-amylase and α-glucosidase inhibitory activity is common to most (summarized in Table 5). Extracts from *Laminaria japonica* (Peng et al., 2011), *Laminaria digitata* (Zaharudin et al., 2018), *Undaria pinnatifida* (Zaharudin et al., 2018), *Sargassum serratifolium* (Ali et al., 2017) and *Saragassum heiphyllum* (Hwang et al., 2015), *Alaria marginata* (Kellogg et al., 2014) and *Fucus distichus* (Kellogg et al., 2014) to name a few, have all been shown to possess α-glucosidase and/or α-amylase inhibitory activities over concentration ranges similar to acarbose. Depending upon the extraction methods, the presence of a range of chemical groups including plastoquinones, polysaccharides, phlorotannins and phenolics have been aligned to the enzyme inhibitory effect. However, only a few studies have been able to provide more precise information as to potential candidate molecules present. Detailed chemical analysis of the most potent *F. distichus* extracts revealed

that the dominant phytochemicals present were fucophloroethol structures of between 3 and 18 different phloroglucinol units (Kellogg et al., 2014), while 2,5-dihydroxybenzoic acid was identified as an important compound present in extracts from both *Laminaria digitata* and *Undaria pinnatifida* (Zaharudin et al., 2018) and the plastoquinones sargahydroquinoic acid, sargachromenol and sargaquinoic acid were identified as compounds of interest in *Sargassum serratifolium* (Ali et al., 2017). Perhaps the most studied pure compounds present in brown seaweed are the fucoxanthins, which have been found to be responsible for the α-glucosidase inhibitory activity in extracts from *Undaria pinnatifida* (Zaharudin et al., 2019), and the fucoidans, which have been isolated from several species including *Turbiniaria ornate* (Lakshmana Senthil et al., 2014), *Sargassum wightii* (Kumar et al., 2015) and *Turbinara conoides* (Lakshmana Senthil et al., 2019) and which inhibit both α-glucosidase and α-amylase.

As mentioned above, most seaweeds assessed for enzyme inhibitory activity have been brown seaweeds, however a small number of studies have determined activity in extracts from red and green seaweeds. Two peptides (Gly-Gly-Ser-Lys and Glu-Leu-Ser) were identified as the primary chemicals responsible for α-amylase inhibitory activity present in proteolytic enzyme hydrolysates from the red seaweed *Porphyris* spp. (laver; Admassu et al., 2018), while ethanolic extract from *Eucheuma denticulatum* similarly inhibits α-amylase activity (Balasubramaniam et al., 2016). To our knowledge, only one green seaweed species (*Halimeda macroloba*) has demonstrated inhibitory activity against α-amylase, although no chemical analysis was performed (Chin et al., 2015).

3.1.2 In vivo studies

Attempts to associate the ability of seaweed extracts to inhibit α-glucosidase and/or α-amylase in vitro with an in vivo reduction in post-prandial glucose and insulin levels have been made in a small number of animal studies, with mixed results. Acute administration of a commercially available combined water extract from *Fucus vesiculosis* and *Ascophyllum nodosum*, which was shown to be a more potent inhibitor of both α-glucosidase and α-amylase in vitro than acarbose, was found to blunt the initial increase in blood glucose, without influencing area under the curve, following starch ingestion in normal fed rats (Gabbia et al., 2017). Interestingly, when administered to high fat-fed rats the extract significantly reduced the area under the curve for both insulin and glucose, suggesting that the extract can slow down both the rate of carbohydrate digestion and assimilation. In contrast, while an

ethyl extract of *Ulva fasciata* was found to inhibit α-amylase in vitro in micromolar concentrations, it induced only a moderate decrease in fasting glucose, and had no effect on the area under the curve of a glucose tolerance test, when given over several days to alloxan-induced diabetic mice (Mohapatra et al., 2018). Studies that have utilized purified seaweed-derived compounds (rather than crude extracts) have, however, tended to generate more consistent findings. Heo et al. (2009) studied diphlorethohydroxycarmolol (DPHC), isolated from *Ishige okamurae*, and found that in vitro enzyme (both α-glucosidase and α-amylase) inhibition was achieved at concentrations 2–10 times lower than acarbose, and was equipotent with acarbose at suppressing post-prandial blood glucose and area under the curve following starch ingestion in both normal and streptozotocin-induced diabetic mice. Similarly, dieckol, isolated from *Ecklonia cava*, preferentially inhibits α-glucosidase over α-amylase and reduces post-prandial blood glucose in streptozotocin-induced T2D mice (Lee et al., 2010). Sulfated polysaccharides from *Codium fragile* have been shown to reduce both fasting plasma glucose and the rise in glucose levels after an oral glucose tolerance test, an effect that was associated with a >50% reduction in both plasma and intestinal α-amylase (Kolsi et al., 2018). A study of fucoidan isolated from 11 different species of seaweed found that the enzyme inhibitory activity varied widely between species, and that only fucoidan from *Fucus vesiculosus* exhibited significant (>50%) α-glucosidase (but not α-amylase) inhibition and reduced fasting blood glucose levels in a dose-dependent manner after 3 weeks of administration to db/db mice (Shan et al., 2016). Structure-activity analysis of the different fucoidans revealed that the potency of each fucoidan was associated with the types of glycoside linkages within the molecules. In a direct comparison between fucoidan from *F. vesiculosus* and *A. nodosum*, Kim, Rioux, and Turgeon (2014) identified that enzyme inhibitory activity was not only determined by the time of harvest, but also that there were inter-species differences in both the molecular weight and the sulfate content of the fucoidans, leading to the proposition that fucoidan may exert its enzyme inhibitory activity through electrostatic interaction between the negatively charged sulfate groups of the fucoidan and the enzyme.

3.1.3 Human studies

Even fewer studies have explored the potential of α-amylase/α-glucosidase inhibition by seaweed extracts in humans. A polyphenol-rich (28% polyphenol/67% fucoidan) extract from *Fucus vesiculosus* did

not have any effect on post-prandial glucose control when given acutely to either healthy volunteers (Murray, Dordevic, Ryan, & Bonham, 2018) or to subjects with high fasting glucose levels (Paradis, Couture, & Lamarche, 2011). However, in the latter group there was a decreased insulin response, suggesting that a beneficial effect is only seen when there is existing dysregulation of glucose handling. In contrast, chronic administration of algal-derived phenols have been shown to either have no effect on (Hernandez-Corona, Martinez-Abundis, & Gonzalez-Ortiz, 2014; Lee & Jeon, 2013) or to significantly reduce (Shin, Kim, Park, Lee, & Hwang, 2012) fasting blood glucose levels, although chronic administration of the phlorotannin dieckol did significantly reduced post-prandial glucose levels (Lee & Jeon, 2015). Taken together this suggests that prolonged consumption is required to see any beneficial effect, but, as highlighted in a recent systematic review into the potential anti-diabetic effects of marine algal polyphenols (Murray, Dordevic, Bonham, & Ryan, 2018), existing data is inconsistent and detailed randomized controlled trials are required to determine optimum doses, treatment regimens and, indeed, the preferred algal source and its post-harvest treatment.

From the above it is evident that there is significant potential for the use of seaweed components for management of post-prandial blood glucose. However, there is substantial variation in the selectivity (or lack thereof) for either α-glucosidase or α-amylase inhibition, not only among seaweed species, but also between extracts from the same species. There are multiple reasons for this variability: (i) the extraction process will determine the predominant chemical species within an extract, thus if extracts were to be used as a means of controlling post-prandial blood glucose in Type 2 diabetics, then close attention will be needed to define the precise extraction method to yield the required amounts of active components to achieve relevant in vivo concentrations; (ii) there is a clear seasonal (and probably geographic) influence over the compounds present within each seaweed species, which again would need to be given consideration when preparing extracts for this use; (iii) specific compounds (e.g., fucoidan) that exert inhibitory effects may vary in their chemical structure from species to species. Nevertheless, the research to date shows that progress is being made in terms of identifying extracts or pure compounds that possess inhibitory activity superior to that seen with acarbose (summarized in Table 5) and that also exhibit selective inhibition of α-glucosidase, which may pave the way for a replacement for acarbose to avoid the side effects associated with α-amylase inhibition.

3.2 Insulin-sensitizing activity of algal extracts

Improving insulin sensitivity is perhaps the "Holy Grail" of therapy for the management of T2D, with the two main classes of agents used clinically being the biguanides (e.g., metformin) and the thiazolidinediones ("glitazones" e.g., pioglitazone). Metformin increases insulin sensitivity in vivo, thus reducing plasma glucose concentrations, increasing glucose uptake, and decreasing gluconeogenesis. Although the precise mechanism of action of metformin is not fully elucidated, it has been shown to act via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms although its pharmacology is likely to be more complex involving multi-organ actions and anti-inflammatory actions (Rena, Hardie, & Pearson, 2017). The glitazones on the other hand bind to the nuclear regulatory protein PPAR-γ which influences insulin-sensitive genes to enhance the production of insulin-dependent enzyme mRNAs and improve glucose utilization by the cells. The main targets (summarized in Fig. 2) that have been explored in the search for seaweed extracts with potential anti-diabetic actions include: Insulin Receptor Substrate (IRS-1), which ultimately results in translocation of GLUT4 to the plasma membrane to facilitate intracellular glucose uptake; AMPK, which, in skeletal muscle, induces fusion of GLUT4 vesicles with the plasma membrane (and thus stimulates glucose uptake), stimulates glycolysis by activating phosphorylation of glycogen phosphorylase, and it inhibits glycogen synthesis through inhibitory phosphorylation of glycogen synthase, while in the liver it inhibits gluconeogenesis; protein-tyrosine phosphatase 1B (PTP1B), which is a negative regulator of insulin through dephosphorylation of both the insulin receptor and the activated insulin receptor substrates.

Few studies have investigated the effects of crude algal extracts on insulin sensitivity but have rather focused more on specific compounds, or groups of compounds. Both ethanolic and water extracts from *Sargassum polycystum* were shown to reduce fasting blood glucose (~50% of the metformin response) without influencing plasma insulin levels in a rat model of T2D (high fat/high sugar diet combined with low dose streptozotocin), suggesting that the hypoglycemic effects were due to increased insulin sensitivity rather than an insulinotropic effect (Motshakeri, Ebrahimi, Goh, Matanjun, & Mohamed, 2013). These responses were attributed to antioxidant effects of fucoxanthin (which is abundant in this species), since a reduction in advanced glycation end-products (AGE's) was detected in the treated animals, reflecting a reduction in tissue damage induced by

the diabetic state. In line with this, fucoidan has been shown in a model of non-alcoholic fatty liver disease (NAFLD) to similarly reduce fasting blood glucose and decrease insulin resistance, while at the same time protecting the liver against injury concomitant with a decrease in the expression of inflammatory markers (Heeba & Morsy, 2015). In a murine T2D model, both low molecular weight fucoidan and fucoxanthin independently decreased fasting blood glucose and increased hepatic glycogen, while fucoxanthin (but not fucoidan alone) was also seen to increase the expression of IRS-1, GLUT-4 and PPAR-γ in adipose tissue, representing an insulin-sensitizing action (Lin, Tsou, Chen, Lu, & Hwang, 2017); interestingly, a combination of fucoxanthin and fucoidan exhibited a synergistic effect in the increased expression of these markers of insulin sensitivity.

A dieckol extract from *Ecklonia cava* has also been shown in db/db mice to decrease fasting blood glucose and circulating insulin levels, effects that were associated with a reduction in hepatic glycogen production resulting from decreased G-6-phosphatase activity and a suppression of hepatic glucose regulating genes (e.g., phosphoenolpyruvate carboxykinase; PEPCK) that are known to be over-expressed in T2D (Lee et al., 2012). The extract also reduced both plasma and hepatic lipids, which again may contribute to the improved glucose profile since increased lipids are positively associated with the development of insulin resistance. The hypoglycemic effect of purified dieckol in db/db mice was subsequently shown to be associated with an increase in phosphorylation of AMPK/Akt in the skeletal muscle of these animals (Kang, Wijesinghe, et al., 2013). These findings are corroborated in a zebrafish model of alloxan-induced diabetes in which dieckol was shown to increase Akt activation in skeletal muscle and to improve regulation of hepatic glucose metabolism to a similar extant as that seen with metformin (Kim et al., 2016).

The AMPK/Akt pathway similarly appears to be the target for the insulin-sensitizing effects of other algal extracts, since extracts from both *Laminaria japonica* and *Hizikia fusiforme* increase glucose uptake in C2C12 myotubes (mouse-derived skeletal muscle) via phosphorylation of both PKB and AMPK, a finding that was mirrored in skeletal muscle from high fat/high sugar-fed mice (Kang, Kim, Kang, Lee, & Lee, 2018). Moreover, both ethanolic and water flavonoid-rich extracts from *Enteromorpha prolifera* improved glucose tolerance through alterations in the expression of insulin signal transduction genes, whereby IRSI (suppressed in T2D), phosphatidylinositol 3-kinase (PI3K) and AKT expression (gene and protein) was increased while gene expression of JNK (increased in T2D) was

decreased (Yan et al., 2019). Taken together these findings support the suggestion that algal extracts rich in flavonoids improve glucose metabolism and hepatic glucose uptake via an increase in insulin signaling.

PTP1B overexpression may play a role in insulin resistance and therefore also presents as a potential therapeutic target although, as yet, there are no inhibitors available for clinical studies. Nevertheless, there is increasing interest in the search for novel PTP1B inhibitors from natural sources (Zhao et al., 2018). Several algal-derived bioactive molecules, such as fucoxanthin, sargahydroquinoic acid and sargachromenol, as well as crude algal extracts, have demonstrated activity as PTP1B inhibitors; the breadth of in vitro studies that have revealed this pharmacological action and determined the structural activity relationships of the various chemical groups contained within the extracts is beyond the scope of this review, however this was recently covered in depth in review by Ezzat et al. (2018). Despite the relative abundance of algal-derived PTP1B inhibitors, their potential for exploitation is compromised by the many pleiotropic actions they exhibit. For example, methanolic extract from the brown alga *Hizikia fusiformis* inhibits PTP1B in vitro, but it is also an α-glucosidase inhibitor, a powerful peroxynitrite scavenger and an inhibitor of inducible nitric oxide synthase (Han et al., 2015), which would make any association between PTP1B inhibition and a hypoglycemic effect difficult to make. Moreover, very few algal-derived PTP1B inhibitors have been assessed for their ability to exert an anti-diabetic effect in vivo and the only study we have identified showed that while an extract from *Rhodomelia confervoides* exhibited both in vitro inhibition of PTP1B and reduced fasting blood glucose in vivo in streptozotocin-induced Type 1 diabetic rats (Shi et al., 2008), a direct relationship between the two was not demonstrated. Therefore, while there may be great potential for bioactive molecules isolated from marine algae to be used as structural scaffolds for novel PTP1B inhibitors, a significant gap remains between demonstrating a cause/effect relationship between in vitro PTP1B inhibition and a hypoglycemic/insulin-sensitizing effect. Furthermore, randomized human clinical trials are also needed to determine whether findings from in vivo animal studies can be translated into a positive clinical outcome.

3.3 Stimulation/preservation of insulin secretion by algal extracts

Stimulation of insulin secretion from pancreatic islets or protecting insulin secreting cells from the damaging effects of hyperglycemia, is a further approach to improving glucose homeostasis in T2D although no currently

used clinical agents appear to preserve pancreatic β-cell integrity. In the case of the former, the agent most widely used in the clinic is the sulfonylurea glibenclamide, which stimulates insulin release from pancreatic β-cells by inhibiting the ATP-sensitive potassium channels (K_{ATP}) inhibitory regulatory subunit sulfonylurea receptor 1 (SUR1), resulting in membrane depolarization and the opening of voltage-dependent calcium channels. However, the use of glibenclamide is limited by its potential to induce hypoglycemia and its efficacy in controlling glucose dysregulation is lower than that of metformin.

Extracts from *Sargassum polycystum* administered to rats with T2D induced by a combination of HF/HS and low dose streptozocin has been shown to decrease the extent of the resulting pathological changes in the islet cells, and perhaps more importantly to decrease the number of cells damaged by the induction of T2D (Motshakeri et al., 2014). Similarly, in models of Type 1 (alloxan or streptozotocin induced) diabetes, both *Laminaria japonica* (Long et al., 2012) and *Ecklonia cava* (Kim & Kim, 2012) extracts increased the pancreatic expression of superoxide dismutase, decreased the expression of inducible nitric oxide synthase and improved β-cell index (measure of cell structure) and mass, observations that were accompanied by an increase in serum insulin levels and a reduction in fasting blood glucose. Moreover, *Ecklonia cava* extract was also shown to increase insulin secretion from pancreatic islet cells. Some insight into the underlying mechanism of how the extract acts as a preserver of β-cells comes from studies with dieckol (present in high quantities in *E. cava*), where protection was observed against glucotoxicity in rat insulinoma cells (Lee et al., 2012). As with the in vivo studies with *E. cava* extract, dieckol reduced ROS and NO production by the cells, increased the expression of the antioxidant enzymes superoxide dismutase and catalase and reduced caspase-3 activation, indicating an anti-apoptotic effect. Fucoidan has also been demonstrated to reduce the histopathological changes in pancreatic islets in a rat strain that spontaneously develops non-insulin dependent diabetes and to act as an insulin secretagogue in RIN-SF rat insulin secreting cells. The latter effect appears to be through a cAMP signaling pathway, since phosphodiesterase inhibition abrogated the effects of fucoidan, rather than through a similar mechanism to glibenclamide, since amylin (a glibenclamide inhibitor) did not reverse its effects (Jiang, Yu, Ma, Zhang, & Xie, 2015). Interestingly, when fucoidan was applied in combination with glibenclamide an additive effect was seen, suggesting that a combination of K_{ATP} channel opening and activation of cAMP in pancreatic islets may be an approach to a greater insulin secretion response.

4. Conclusion

Extracts from seaweed and their bioactive compounds have been shown to provide a good source for discovering new therapeutic drugs for obesity and T2D management. Pharmacological interventions focused on maintaining/improving adipose tissue health and liver energy metabolism, modulating the diversity of gut microbiota, regulating glucose absorption from the intestine, and improving insulin sensitivity/secretion therefore form the basis for novel therapeutic interventions in obesity, T2D and metabolic diseases.

The molecular mechanisms affected by seaweed extracts and bioactive compounds are specific to different tissues and for obesity or T2D management, however key signaling pathways or targets have emerged. In obesity, modulation of antioxidant capacity and reduction of intracellular ROS levels within tissues, and regulation of signaling pathways involved in enhancing browning of white adipose tissue, have been highlighted as important mechanisms and potential targets for optimal energy metabolism. In T2D, management of post-prandial blood glucose by modulating α-glucosidase or α-amylase activities, modulation of AMPK signaling pathway, and similarly to obesity, reduction of ROS and NO production with subsequent increased expression of antioxidant enzymes have been shown to play a key role in glucose metabolism and insulin signaling.

Future studies aimed at discovering new therapeutics drug from marine natural products should, therefore, focus on bioactive compounds from seaweed that exert antioxidant properties and regulate the expression of key signaling pathways, which are common mechanisms to both obesity and T2D management. In addition, considering the paucity of data around the clinical benefits of seaweed-derived compounds in obesity and T2D, it is clear that a substantial effort, in the form of human clinical trials, is required.

Conflict of interest

C.W., G.B. and T.S. have no conflict of interest. F.H. is an employee of Algaia, which is a company that produces natural seaweed extracts and solutions.

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