

The Potential Applications of Marine Bioactives Against Diabetes and Obesity

Hang Wang, Zhi-ming Fu, Chun-chao Han *

School of Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan, P. R.China

*Corresponding author: shandongtcmh@163.com

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Abstract Diseases caused by metabolic dysfunction such as diabetes and obesity have serious effect on human's health. Hence, it's important for human to find effective functional food or drugs against metabolic dysfunction. The marine environment represents a relatively untapped source that can be applied to various aspects. Meanwhile, numerous marine-based compounds have been identified as having diverse biological activities, with some reported to interfere with the pathogenesis of diseases. On the basis of their bioactive properties, this review focuses on the potential use of marine-derived compounds to against metabolic dysfunction, including diabetes and obesity.

Keywords: marine bioactives, diabetes, obesity, metabolic dysfunction

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1. Introduction

Metabolic disease, including dyslipidemia and diabetes, constitutes a major emerging health crisis in the world. The WHO, in the 2009 report, states that high blood plasma ranked first in the list of leading global risks for mortality and accounted for 7.5 million deaths in the world in 2004. According to MetS concept, elevated blood plasma is clustered with other symptoms, including obesity, dyslipidemia, and glucose dysregulation. The metabolic syndrome (MetS) is a combination of medical disorders integrated to have a useful description of related cardiovascular risk factors which also predict the risk of developing diabetes (Figure 1). Diabetes, which is diagnosed based on blood plasma hyperglycemia, has been linked to lipid overload and abdominal obesity and may synergize with these conditions to promote negative clinical outcomes [1,2]. Although the symptoms and clinical pathology and physiology of these conditions are well understood, the question of pharmacologic treatment of dyslipidemia and diabetes remains unresolved well. Thus, the novel therapeutic strategies are extensively sought. From the point of view of "self-medication" or "preventive medicine," several dietary supplements are used in the prevention of life-style related diseases including metabolic disturbances.

The marine world, due to its phenomenal biodiversity, is a rich natural resource of many biologically active compounds such as polyunsaturated fatty acids (PUFAs), sterols, proteins, polysaccharides, antioxidants and pigments. Many marine organisms live in complex habitats exposed to extreme conditions and, in adapting to new environmental surroundings, they produce a wide

variety of secondary (biologically active) metabolites which cannot be found in other organisms [3]. Numerous marine bioactives have been recently identified, whose several biological activities could interfere with the pathogenesis of many diseases. Therefore, to facilitate discussion of this issue, the following review examines the existing scientific knowledge which demonstrates the suitability of marine-derived bioactive compounds to against metabolic dysfunction.

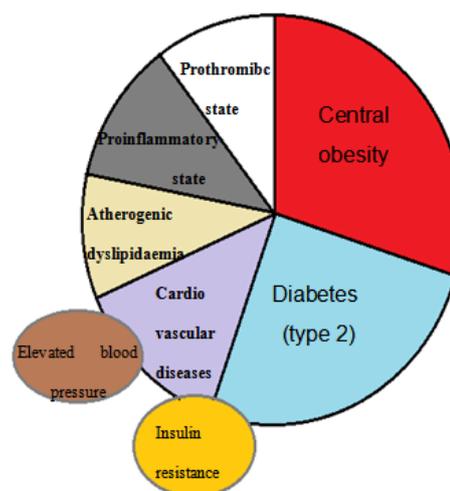


Figure 1. General Features and Diseases of MetS

2. Bioactive Compounds from Marine Organisms and the Effects

People worldwide know that marine foods participate in human health promotion. A diet rich in marine products is

considered to result in a lower incidence of diabetes, cancer and obesity. To date, many of reports have also showed that bioactive compounds from marine organisms,

including Fucoxanthin, Astaxanthin, Marine Collagen Peptides, Dieckol and Krill Oil, exert a positive influence on metabolic dysfunction (diabetes and obesity) (Figure 2).

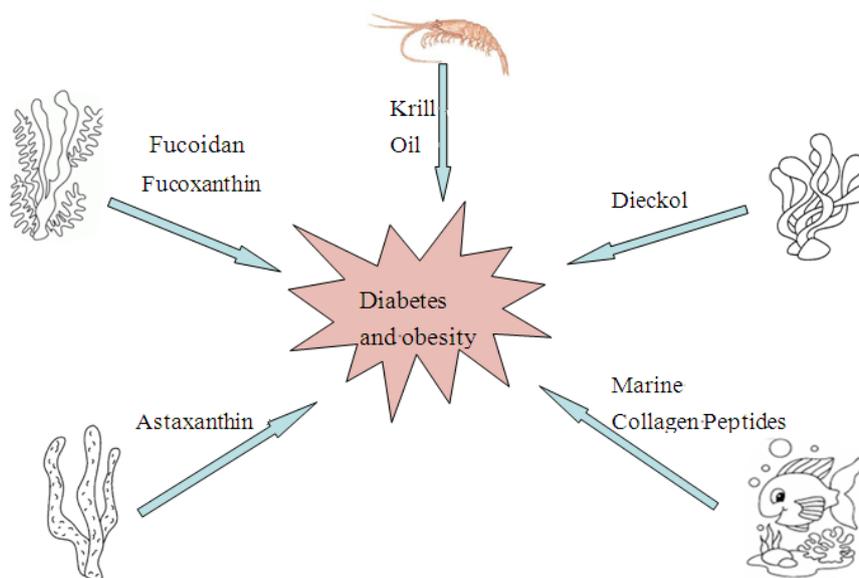


Figure 2. Bioactive compounds from marine organisms against metabolic dysfunction

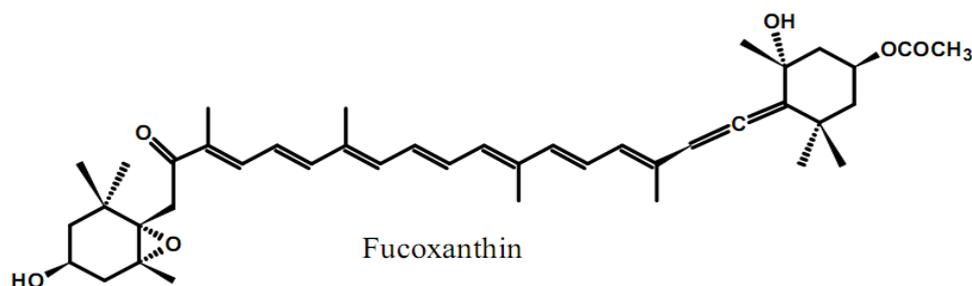


Figure 3. Chemical structures of Fucoxanthin

2.1. Fucoxanthin

Fucoxanthin (Figure 3) is an orange-colored pigment, along with chlorophylls a and c and β -carotene, and contributes more than 10% of the estimated total production of carotenoids in nature, especially in the marine environment [4,5]. Fucoxanthin is mainly isolated from the marine brown seaweeds such as brown seaweeds (*Phaeophyceae*) and diatoms (*Bacillariophyta*). Some studies have showed that fucoxanthin and its metabolites have a great antidiabetic activity, antioxidant activity, anti-cancer, anti-diabetic and anti-photoaging properties [6,7,8].

2.1.1. Antidiabetic Activity

Insulin resistance in peripheral tissue is one of the major pathogenic characteristics of type 2 diabetes. The results of a recent work suggested that there was a remarkable reduction in the plasma insulin level in KK- A^y mice fed 0.2% fucoxanthin, comparing with the control mice [6]. Furthermore, it also showed the blood glucose and plasma insulin concentration were more significantly decreased by the combination diet of 0.1% fucoxanthin and 6.9% fish oil along with down-regulating TNFR mRNA and attenuated the weight gain of WAT [6].

Additionally, Nicolantonio D'Orazio et al. [7] demonstrated that fucoxanthin (FX) and its metabolites prevented the development of diabetes through down-regulation of MCP-1, TNF- α , IL-6 and PAI-1 mRNA expression in a model of obese/diabetic mice (KK- A^y), but not in lean C57BL/6J mice. In addition, FX promoted the recovery of blood glucose uptake to muscle by the up-regulation of glucose transporter 4 (GLUT4) mRNA expression, which is also related to the antidiabetic effect [7]. FX is regarded as an anti-obesity and anti-diabetic functional food and even provided other health benefits, which is proved safe with no side effects [9,10,11,12].

2.1.2. Anti-obesity Activity

The anti-obesity effects of fucoxanthin have been studied in diet-induced obesity mice fed a high-fat diet. Myoung-Nam Wool et al. [13] researched a possible mechanism about the anti-obesity effects of fucoxanthin with two doses in diet-induced obese mice. At last, they found that fucoxanthin significantly down-regulated various lipogenic enzyme activities in epididymal adipose tissue with a simultaneous decrease in fatty acid β -oxidation activity, suggesting that the anti-obesity effect of fucoxanthin could be mediated by altering lipid-regulating enzymes and UCPs in the visceral fat tissues

and plasma adipokine levels [13]. An ethanol extract of fucoxanthin-rich seaweed was examined for its effectiveness as a nutraceutical for body fat-lowering agent and for an antiobese effect based on mode of actions in C57BL/6J mice. In the end, results of this study indicated that Fx-SEE significantly reduced body and abdominal white adipose tissue (WAT) weights, plasma and hepatic triglyceride (TG) and alters hepatic cholesterol metabolism, FA synthesis and lipid absorption [14]. In addition, the effects of combined fucoxanthin (Fc) and conjugated linoleic acid (CLA) were also investigated and the results suggested that Fc and the combination of Fc plus CLA could reduce serum levels of triacylglycerol, glucose and leptin, and the combination could exert anti-

obesity effects by regulating mRNA expression of enzymes related to lipid metabolism in WAT of diet-induced obesity rats [15].

2.2. Astaxanthin

Astaxanthin (ASX) (Figure 4), a xanthophyll carotenoid, can be found in the marine algae *Hematococcus pluvialis*, *Chlorella zofingiensis*, and *Chlorococcum sp.*, and the red yeast *Phaffia rhodozyma*. Numerous studies have shown that astaxanthin has powerful antioxidant, anti-tumor, anti-diabetic, anti-inflammatory and cardioprotective properties [16-21].

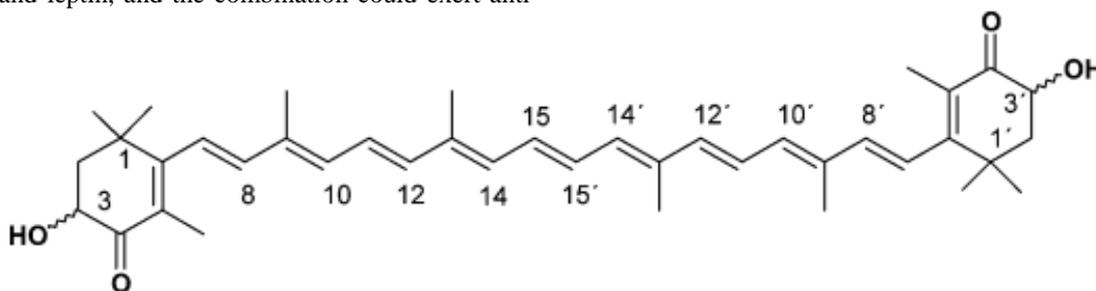


Figure 4. Chemical structures of Astaxanthin

2.2.1. Antidiabetic Activity

Elumalai Arunkumar et al. [18] investigated the mechanisms underlying the insulin sensitivity effects of ASX in a non-genetic insulin resistant animal model. The results showed that ASX improved insulin sensitivity by activating the post-receptor insulin signaling, *i.e.* enhancing the autophosphorylation of insulin receptor- β (IR- β), IRS-1 associated PI3-kinase step, phospho-Akt/Akt ratio and GLUT-4 translocation in skeletal muscle [18]. Oxidative stress induced by hyperglycemia possibly causes the dysfunction of pancreatic β -cells and various forms of tissue damage in patients with diabetes mellitus [19]. It was found that astaxanthin could diminish the oxidative stress caused by hyperglycemia in the pancreatic β -cells, significantly improve glucose tolerance, increase serum insulin levels, and decrease blood glucose levels. Recently, Bhuvaneshwari et al. [20] demonstrated that astaxanthin could substantially improve insulin sensitivity through abolishing significant elevation in both glucose and insulin levels induced by a high fat plus high fructose diet in mice.

But beyond that, Hussein et al. [21] researched the effects of astaxanthin in a metabolic syndrome animal model of spontaneously hypertensive corpulent rat. And the results showed that astaxanthin markedly decreased the levels of blood glucose, triglycerides and nonesterified fatty acids, and significantly increased the levels of high-density lipoprotein cholesterol and adiponectin. It is suggested that astaxanthin ameliorates insulin resistance and improve insulin sensitivity by increasing glucose uptake, and by modulating the levels of circulating adiponectin and blood lipids [21].

2.2.2. Anti-obesity Activity

ASX has been investigated the effects of anti-obesity in obese mice fed a high-fat diet. Then, the results showed that ASX inhibited the increases in body weight and

weight of adipose tissue, whereas reduced liver weight, liver triglyceride, plasma triglyceride, and total cholesterol [22]. Oxidative stress is caused by an imbalance between the antioxidant and the reactive oxygen species, which results in damage to cells or tissues, and has been reported to involve in obesity. Hye Duck Choi et al. [23] investigated the effect of ASX, which is known to be a potent antioxidant, on oxidative stress in overweight and obese adults in Korea. Malondialdehyde (MDA), isoprostane (ISP), superoxide dismutase (SOD) and total antioxidant capacity (TAC), as oxidative stress biomarkers, were measured at baseline after ASX administration in two dose groups (ASX 5mg and 20mg once daily for 3 weeks). The data showed the MDA (by 34.6% and 35.2%) and ISP (by 64.9% and 64.7%) levels were significantly lowered, whereas SOD (by 193% and 194%) and TAC (by 121% and 125%) levels were significantly increased in two dose groups [23].

2.3. Marine Collagen Peptides

Marine collagen peptides (MCPs) are compounds of low-molecular-weight peptides derived from the skin of deep-sea fish like chum salmon (*Oncorhynchus keta*) by enzymatic hydrolysis. The various multifunctional properties of MCP have been described already, including extending the life span, antidiabetic activity, antioxidative activity, anti-hypertension, anti-skin ageing, anti-ulcer and could improve lipid metabolism [24-30].

2.3.1. Antidiabetic Activity

Cui-Feng Zhu et al. [25] examined effects of MCPs on markers of PPARs, LXRs, and FXRs in type 2 diabetic patients with/without hypertension, and found that levels of free fatty acid, hs-CRP, resistin and Prostacyclin decreased significantly in diabetics, indicating that MCPs could offer protection against diabetes and hypertension by affecting levels of molecules involved in diabetic and hypertensive pathogenesis. In addition, they also

examined the effects of MCPs on glucose and lipid metabolism in Chinese patients with type 2 diabetes mellitus (T2DM) and primary hypertension. The results showed that MCPs significantly reduced levels of fasting blood glucose, HbA1c, diastolic blood pressure, mean arterial pressure and creatinine but increased levels of Insulin Sensitivity Index and Insulin Secretion Index, indicating that MCP treatment could improve glucose and lipid metabolism in diabetic patients [31,32].

2.4. Polyphenol

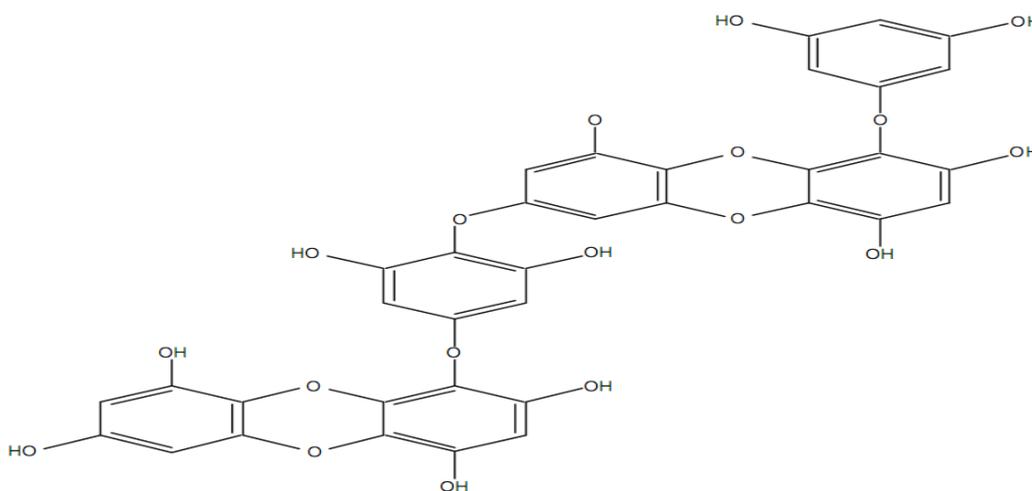


Figure 5. Chemical structures of Dieckol

2.4.1. Antidiabetic Activity

Min-Cheol Kang et al. [34] investigated the attenuation of type II diabetes by dieckol through administering intraperitoneal injection of dieckol in C57BL/KsJ-db/db, a type II diabetes mouse model. The results of this study showed that the blood glucose level, serum insulin level and body weight were significantly reduced in the dieckol administered group, compared to that of the saline administered group [34]. Furthermore, dieckol reduced thiobarbituric acid reactive substrates (TBARS), as well as increased activities of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-px) in liver tissues [34]. Pancreatic β cells are very sensitive to oxidative stress and this might play an important role in β cell death with diabetes. Seung-Hong Lee et al. [35] studied the protective effect of dieckol against high glucose-induced oxidative stress by using rat insulinoma cells and human umbilical vein endothelial cells (HUVECs). And they found that dieckol dose-dependently reduced the level of thiobarbituric acid reactive substances (TBARS), the generation of intracellular reactive oxygen species (ROS), and the nitric oxide increased by a high glucose concentration [35,36].

2.4.2. Anti-hyperlipidemic Effect

Phlorotannins isolated from *Ecklonia cava* exhibit various beneficial biological activities such as antioxidant, anticancer, antidiabetic, anti-human immunodeficiency virus, antihypertensive, matrix metalloproteinase enzyme inhibition, hyaluronidase enzyme inhibition, radioprotective, and antiallergic activities [37]. Yuxi Wei

Dieckol (Figure 5), a kind of phlorotannin, is a marine algal polyphenolic compounds that has been isolated from brown seaweed *Ecklonia cava*. Previously, several evidences have demonstrated that supplementation of *E. cava* extracted showed anti-diabetes effect by hepatic glucose and lipid metabolism through the improvement of insulin sensitivity in type II diabetes in a *db/db* mouse model [33]. And dieckol exhibits strong antioxidant activity and protections.

et al. chose high molecular weight phlorotannins from *Sargassum thunbergii* (HMPs) to explore the regulating mechanism on blood lipid regulation. Results of the study showed that HMPs could obviously increase liver LDL-R level, as well as significantly decrease TC, TG levels and LDL-C level [38]. Additionally, eckol and dieckol isolated from ethanolic (EtOH) extracts of *Ecklonia stolonifera* induced a significant reduction in serum TG, TC, and LDL-C levels, as well as in the atherogenic index (A.I.). Moreover, treatment with dieckol was more effective than eckol [39].

2.5. Krill Oil

Krill oil (KO) is extracted from Antarctic krill, *Euphausia superba*, a zooplankton crustacean rich in phospholipids carrying long-chain omega-3 PUFAs, mainly EPA and DHA. Additionally, Krill oil also contains various potent antioxidants, including vitamins A and E, astaxanthin, and a novel flavonoid similar to 6, 8-di-c-glucosylluteolin, but with two or more glucose molecules and one aglycone [40]. To this day, KO has been discovered to have various beneficial effects, including inhibition of hepatic steatosis [41,42], anti-inflammation [43,44], antioxidation [44,45], antihyperlipidaemic effect [42,46], antihyperglycaemic effect [42], modulation of the endocannabinoid system [47,48] and cardioprotective effect [49].

2.5.1. Antidiabetic Activity

Krill oil (KO) is rich in n-3 fatty acids, phospholipid (PL) and triglyceride (TG), which could be responsible either individually or in combination for the marked improvements observed in lipid and glucose metabolism

[50]. Sally Tandy et al. researched and found that KO supplementation significantly reduced fasting blood glucose and increased serum adiponectin levels, indicating that dietary KO has a beneficial effect on lipid and glucose metabolism in experimental mice with diet-induced obesity and insulin resistance [50].

2.5.2. Anti-obesity Activity

It has been reported that krill oil decreased significantly body weights, total cholesterol (TC), LDL-cholesterol (LDL-C) and Triglycerides (TG) in serum of hyperlipidemia rats [51]. Dong-Mei Li et al. assessed the effects of whole krill oil (WKO) and phospholipid-type krill oil (PKO) on plasma cholesterol in Wistar rats fed a high-cholesterol diet (HCD), which were extracted with hexane and ethanol respectively, and suggested that the intake of PKO and WKO for caused a significant reduction in body weight gain and plasma levels of TC and LDL-C in HCD-fed rats. Compared with WKO, PKO was more effective to decrease plasma TC and LDL-C levels [52].

Meanwhile, some clinical studies also demonstrated that Krill oil could reduce the level of glucose, total cholesterol, triglycerides, LDL and HDL, and could increase plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with no indication of adverse effects on safety parameters. Furthermore, the results showed that the effects of krill oil on the clinical course of hyperlipidemia were more effective than fish oil [53,54].

As is well known, the endocannabinoid system is deeply correlated with the regulation of the homeostasis of body composition by regulating food intake and energy expenditure [55]. Sebastiano Banni et al. [56] investigated the effect of the intake of KO for four weeks on endocannabinoid system in over weight and obese subjects. The results confirmed KO was able to significantly decrease 2-arachidonoylglycerol (2-AG). In addition, they found the decrease of 2-AG was correlated to the plasma n-6 /n-3 phospholipid long chain polyunsaturated fatty acid (LCPUF A) ratio and relatively low doses of LCPUFA n-3 as KO could significantly decrease plasma 2-AG levels in obese subjects [56].

2.6. Polysaccharide

Fucoidan, a sulfated fucose containing polysaccharide, was purified from marine brown algae including *Fucus vesiculosus*, *Laminaria japonica* and *Undaria pinnatifida*. It was reported that had a variety of biological activities, containing antioxidant, anti-HIV and antitumor activities [57,58]. Recently, there has been increasing interest in potential biological activities against fat and blood glucose inhibition from fucoidan.

2.6.1. Antidiabetic Activity

Fucoidan consists of L-fucose together with xylose, galactose and mannose, which has been broadly studied for its numerous biological closely related to molecular weight. Kui-Jin Kim et al. [59] studied the effects of different molecular weight forms (5 kilodalton (k), 5–30 k and crude) of fucoidan on oral glucose tolerance tests in mice. The blood glucose was most strongly suppressed and insulin sensitivity was improved due to fucoidan.

Thus, the results demonstrated that low molecular weight fucoidan (LMWF) prevents hyperglucemia on diabetes that depend on its molecular weight [59]. Beyond that, Yong-Tae Jeong et al. [60] also investigated the metabolic effects of LMWF in obese diabetic mice with oral administration 6 weeks. After determining the blood glucose levels, total cholesterol levels, fat adiponectin contents and related indicators in blood samples or tissues, it showed that LMWF improves glucose homeostasis and lipid profiles in db/db mice and endoplasmic reticulum stress-induced insulin resistance in L6 myotubes in a manner similar to metformin [60].

2.6.2. Anti-obesity Activity

Fucoidan extracted from the brown seaweeds, which has a higher sulfate content was reported that possessed potential anti-obesity effects [61] and anti-inflammatory activity in several cell lines [62]. Nevertheless, it is still unclear whether fucoidan would be beneficial in adipogenesis. Then, to test their hypothesis of fucoidan extracted from the sporophyll of *U pinnatifida* exerting anti-obesity effects, Kui-Jin Kim et al. determined the obesity-specific therapeutic action of fucoidan in 3T3-L1 adipocytes [63]. Then, those findings suggested that fucoidan could be useful for the prevention or treatment of obesity due to its stimulatory lipolysis and reduction of the accumulation of lipids [64,65].

3. Other Marine Active Compounds

There is also many other marine active compounds, due to the marine world phenomenal biodiversity, except above described. For example, hyrtiosol, from the marine sponge *Hyrtios erectus*, has been discovered to inhibit protein tyrosine phosphatase 1B (PTP1B) activity in dose-dependent fashion, negatively regulating insulin signaling, and enhance the membrane translocation of the key glucose transporter Glut4 in PTP1B-overexpressed CHO cells [66].

In addition, Kim et al. [67] reported the marine natural products sargaquinoic acid (SQA) and sargahydroquinoic acid (SHQA) from *Sargassum yezeense* as novel PPAR α/γ dual agonists, which increased adipocyte differentiation accompanied by increased expression of adipogenic marker genes, suggesting that these PPAR α/γ dual agonists may reduce insulin resistance through regulation of adipogenesis.

4. Conclusion

To date, more and more metabolic diseases have influenced in human's health and quality of life. The sea is a rich source of useful compounds with new chemical structures and pharmacological effects: significant immunomodulation (against allergy), anti-inflammatory (and as a consequence, antitumor and analgesic), antibacterial and antiviral activities [61]. A large amount of activity compounds, including fucoxanthin, astaxanthin, marine collagen peptides, dieckol, Krill oil and fucoidan, have been already researched to against metabolic dysfunction such as diabetes and obesity (Table 1). Moreover, the effects of marine bioactive compounds

showed no toxicity and side effects. Marine bioactives could potentially develop as functional food or drugs, since their biological activities appear to influence the pathogenesis and the clinical course of several metabolic

diseases. In conclusion, further research should go in this direction in order to show new preventive and potential therapeutic strategies against metabolic dysfunction.

Table 1. Antidiabetic and anti-obesity properties of marine natural products with established mechanisms of action

Compound	Source	Effects/Mechanism of action	Reference
Fucoxanthin	brown seaweeds	Antidiabetic/ Anti-obesity Activity	[6,7,13,14,15]
Astaxanthin	marine algae	Antidiabetic/ Anti-obesity Activity	[18-23]
Marine collagen peptides	deep-sea fish	Antidiabetic Activity	[25,31,32]
Dieckol	<i>Ecklonia cava</i>	Antidiabetic/ Anti-hyperlipidemic Effect	[34-39]
Krill oil	Antarctic krill	Antidiabetic/ Anti-obesity Activity	[50-56]
Fucoidan	marine brown algae	Antidiabetic/ Anti-obesity Activity	[59-65]
Hyrtilial	marine sponge	Inhibit protein tyrosine phosphatase 1B (PTP1B) activity	[66]
SQA and SHQA	<i>Sargassum yezoense</i>	Reduce insulin resistance	[67]

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