Bioactive compounds from marine macroalgae and their hypoglycemic benefits

Chao Zhao[1,2,5], Chengfeng Yang[1], Bin Liu[1], Luan Lin[5], Satyajit D. Sarker[3], Lutfun Nahar[3], Hua Yu[4], Hui Cao[4], Jianbo Xiao[4*]

[1]College of Food Science, Fujian Agriculture and Forestry University, Fuzhou 350002, China

[2]Department of Chemistry, University of California, Davis 95616, USA

[3]Medicinal Chemistry and Natural Products Research Group, School of Pharmacy and Biomolecular Sciences, Faculty of Science, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool L3 3AF, UK

[4]Institute of Chinese Medical Sciences, State Key Laboratory of Quality Control in Chinese Medicine, University of Macau, Macau SAR, China

[5]Fujian Province Key Laboratory for the Development of Bioactive Material from Marine Algae, Quanzhou Normal University, Quanzhou 362000, China

[*]To whom correspondence should be addressed: Jianboxiao@yahoo.com

Abstract: Diabetes mellitus is a group of chronic metabolic disorders characterized by hyperglycemia due to defects in insulin action and/or secretion. It is a worldwide problem which has led to illness and premature mortality for many people, and the number of diabetes cases has been rising sharply. Unluckily, many conventional antidiabetic agents either show limited efficacy or serious mechanism-based side effects. Marine macroalgae possess tremendous nutritional value and have been well-known to cure and prevent diabetes. An increased interest in various bioactive natural products from marine macroalgae, as a potential source of effective antidiabetic agents, has been observed in recent years. The effects of macroalgae may delay the development of diabetes and alter the metabolic abnormalities through various mechanisms of actions. This review provides an overview of marine macroalgae used to prevent and manage diabetes and explores the hypoglycemic properties of macroalgae-derived bioactive compounds such as polyphenol, bromophenols, sulfated polysaccharides, fucoidan, fucosterol, phlorotannins, carotenoid pigments and fucoxanthin with their probable mechanisms behind hypoglycemic activity.

Keywords: Phaeophyta; rhodophyta; chlorophyta; bioactive compounds; hypoglycemic activity

1. Introduction

Globalization, industrialization, and changes of human environment, behavior and lifestyle have led to increasing raising rates of both obesity and diabetes (Xiao & Högger, 2015). Diabetes mellitus, one of the most important global health problems, was estimated as the fifth leading cause of death globally (Roglic et al., 2005). The International Diabetes Federation (IDF) estimated that the number of diabetes cases is expected to grow to 438 million globally in 2030 from 285 million people in 2009 (Atlas, 2009). It is a serious chronic disease characterized by hyperglycemia due to defects in insulin action, insulin secretion, or both of them (ADA, 2015). The main characteristic symptoms of diabetes are polyuria, polydipsia and polyphagia (ADA, 2005). The varying degrees of insulin resistance (Pontiroli, 2004) and postprandial hyperglycemia play an important role in the development of type 2 diabetes and related complications (Lee et al., 2012). An effective control of postprandial blood glucose level play key role in diabetes care which can improve the life quality of patients with type 2 diabetes. A number of pharmacological approaches have been used to control diabetes based on the different modes of action such as stimulation of insulin release, increase in glucose transport activity, inhibition of gluconeogenesis, and reducing absorption of glucose from the intestine (Thilagam, Parimaladevi, Kumarappan, & Mandal, 2013). Currently available therapies, including insulin and various oral antidiabetic agents, have been used as monotherapy or in combination to make a better glycemic regulation (Jung et al., 2006). However, a number of those antidiabetic agents either have inadequate efficacy or serious mechanism-based side effects (Lee et al., 2014). Thus, the search and investigation for more effective and safer hypoglycemic agents from natural sources has continued to be an important issue (Vinayagam, Xiao, & Xu, 2017).

Owing to the rich biodiversity, the marine environment is a vast and relatively untapped source for new bioactive ingredients including polyunsaturated fatty acids, polyphenol, sterols, proteins, sulfated polysaccharides, antioxidants and pigments (Lee, Ko, Kang, Lee, & Jeon, 2016; Suleria, Gobe, Masci, & Osborne, 2016; Manikkam, Vasiljevic, Donkor, & Mathai, 2016; Saleh, Zhang, & Shen, 2016; Ruocco, Costantini, Guariniello, & Costantini, 2016). Marine algae, the primary producers of all aquatic ecosystems, have served as important sources of bioactive natural substances including antidiabetic, antioxidant,

antibacterial and antivirals agents (Choochote, Suklampoo, & Ochaikul, 2014; Zhao, Wu, Yang, Liu, & Huang, 2015). In particular, macroalgae are well-known healthy food with naturally rich in minerals and dietary fibers. Marine algae are consumed as a regular part of traditional diet in the Far East and Hawaiian Islands, Japan, Korea, and China. There are about 9,000 species macroalgae have been broadly classified into three categories according to their composition of pigments, i.e., Phaeophyta, Rhodophyta and Chlorophyta (or the brown, red, and green algae, respectively) (Khan et al., 2009). Diverse classes of unique metabolites have shown numerous biological activities and potential health benefits (Pangestuti & Kim, 2011), such as anticancer, antidiabetic, antihypertensive, antihyperlipidemic, antioxidant, anticoagulant, anti-inflammatory, anti-estrogenic, antiviral, antifungal, antibacterial, immunomodulatory, neuroprotective, and tissue healing properties *in vivo* (Mohamed, Hashim, & Rahman, 2012). With the identification of a large number of bioactive compounds from marine macroalgae, e.g., sulfated polysaccharides, phlorotannins and diterpenes, an increased level of attention has been given recently to study the potential applications of macroalgae and their components as functional ingredients for both human and animal health (Gupta & Abu-Ghannam, 2011). Functional ingredients of macroalgae have been found to possess antidiabetic properties and are typically used as food supplements (Pangestuti & Kim, 2011). This review paper pay close attention to the potential applications of marine macroalgae and/or macroalgae-derived bioactive compounds in diabetes management (Table 1), and also discusses their possible mechanisms of action.

2. Phaeophyta (brown algae)

2.1 *Pelvetia* Decne. & Thur.

Pelvetia is the genus of typical marine macroalgae, and comprises only four species. *Pelvetia siliquosa* C.K.Tseng & C.F.Chang has been reported to self-grow on the craggy surfaces near the seashores of the southern area (Lee, 2003). Fucosterol (**1**), isolated from *P. siliquosa,* was shown to decrease serum glucose levels and to inhibit glycogen degradation in streptozotocin (STZ)-induced diabetic rats (Lee, Shin, Kim, & Lee, 2004). An extract from *P. babingtonii* (Harvey) de Toni (Fucaceae) exhibited potent α-glucosidase inhibitory activity and was effective for suppressing postprandial hyperglycemia (Ohta, Sasaki, Oohori,

Yoshikawa, & Kurihara, 2002). α-Glucosidase, an enzyme located in the brush-border membranes of human intestinal cells, is involved in carbohydrate metabolism and post-translational processing of glycoprptein (Li, Niu, Fan, Han, & Zhang, 2005). Similarly, α-amylase is a kind of main secretory products of the pancreas and salivary glands, constituting a family of endoamylases that plays a vital role in the digestive system and catalyses the initial step in hydrolysis of starch to a mixture of smaller oligosaccharides through the cleavage of α-D (1–4) glycosidic bonds (Kandra, 2003). α-Glucosidase and α-amylase have long been recognized as preferred drug targets for the modulation of postprandial hyperglycemia (Liu, Zhang, Wei, & Lin, 2011). Some marine macroalgae may be considered as natural inhibitors of α-glucosidase and α-amylase and be used as auxiliary hypoglycemic functional foods or drugs (Rengasamy, Kulkarni, Stirk, Van Staden, 2014).

2.2 *Ecklonia* Hornemann

Several *Ecklonia* species contain high levels of marine algal polyphenols (Yoon et al., 2013). Polyphenols are one of the main classes of secondary metabolites found in terrestrial plants and marine macroalgae, but there are fundamental differences in the chemical structures of polyphenols found in both terrestrial and marine plants (Lee & Jeon, 2013). The methanolic extract of *Ecklonia stolonifera* Okamura, a brown alga belonging to the algal family Lessoniaceae*,* has rich polyphenol content, which were shown strong inhibition effect on α-glucosidase activity *in vitro* as well as strong suppression of the increase in plasma glucose level and lipid metabolism in diabetic KK-Ay mice. The bioactive compounds were investigated to be phlorotannins (Gouveia et al., 2007; Iwai, 2008). Phlorotannins are polyphenols which widely occur in marine organisms, especially in brown macroalgae (Yotsu-Yamashita et al., 2013). A review have outlined various antidiabetic mechanisms associated with phlorotannins from brown algae (Lee & Jeon, 2013). Phlorotannins from *E. kurome* Okamura showed inhibitory activities against carbohydrate-hydrolyzing enzymes *in vitro* and decreased postprandial blood glucose levels *in vivo* (Xu et al., 2012). Before that, *Eisenia bicyclis* (Kjellman) Setchell, *Ecklonia stolonifera* and phlorotannins isolated from them, namely dieckol (**2**), eckol (**3**), 7-phloroeckol (**4**), and phlorofucofuroeckol-A (**5**) were shown to possess marked α-glucosidase and protein tyrosine phosphatase 1B (PTP1B)

inhibitory activities (Moon et al., 2011). Moreover, the insulin receptors are back to their original state via the activity of protein tyrosine phosphatases (PTPs) (Wälchli, Curchod, Gobert, Arkinstall, & van Huijsduijnen, 2000). PTP1B is a member of PTPs family that have been isolated and identified from mammalian cells, and it maintains the balance of protein tyrosine phosphorylation with protein tyrosine kinases (PTK). Cicirelli et al. (1990) reported that PTP1B was associated with insulin signal transduction for the first time. It has been established that PTP1B played an important role as a negative regulator of the insulin signalling pathway. Another study showed that a PTP1B knock-out mouse had increased insulin sensitivity (Elchebly et al., 1999). Several clinical studies have revealed that PTP1B is mainly responsible for dephosphorylation of the activated insulin receptor and thus down regulates insulin signaling, which can be an effective target for the therapy of type 2 diabetes (Zhang & Zhang, 2007).

Several known phloroglucinol derivatives isolated from *E. cava* Kjellman, e.g., dieckol (**2**), 7-phloroeckol (**4**), phlorofucofuroeckol-A (**5**), 6,6-bieckol (**6**), and fucodiphloroethol-G (**7**), possess significant inhibitory activities against α-amylase and α-glucosidase (Lee, Karadeniz, Kim, & Kim, 2009). Dieckol (**2**) not only inhibits the activities of α-glucosidase and α-amylase but also alleviates postprandial hyperglycemia and improve insulin sensitivity *in vivo* (Lee et al., 2010; Pontiroli, 2004). Dieckol (**2**) and the extract of *E. cava* can also offer the anti-diabetic effect through activating both adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) and Akt kinase signal pathways (Kang et al., 2010; Kang et al., 2012). Adiponectin activates the downstream target AMPK which is a serine/threonine kinase that plays an important role in energy metabolism at both the cellular and whole-organism levels (Hardie, 2008; Padmalayam & Suto, 2013). AMPK controls whole-body glucose homeostasis by regulating metabolism in multiple peripheral tissues, and its activation induces the expression of PPARα and carnitine palmitoyltransferase I (CPT-1) that increase fatty acid oxidation and improve insulin sensitivity (Bijland, Mancini, & Salt, 2013; Long & Zierath, 2006). Taking all these into account, it can be assumed that *E. cava* may have the potential as an AMPK activator to increase the expression of AMPK, thus controlling balance of blood glucose. However, there are only limited number of studies have investigated the role of macroalgae or macroalgae-derived compounds on activation of AMPK.

2.3 *Laminaria* J.V.Lamouroux

Laminaria japonica J.E.Areschoug is one of the most important marine medicinal foodstuffs (Shirosaki & Koyama, 2011). Its rhizoid has long been applied as a traditional medicine for diabetes mellitus in China. Butyl-isobutyl-phthalate (**8**), extracted from *L. japonica*, exhibited hypoglycemic effect *in vivo* and non-competitive inhibition of α-glucosidase *in vitro* (Liu, Zhang, Qin, & Lin, 2011). The synthesized butyl-isobutyl-phthalate (**8**) bound with α-glucosidase and induced conformational changes of the enzyme, thus providing a potential to develop new α-glucosidase inhibitors (Liu, Zhang, Qiu, & Lin, 2011). However, further studies are needed to confirm those findings. Over the past decades, *L. japonica* is a rich source of various functional compounds with diverse biological properties; among those, polysaccharides including alginate, fucoidan and laminaran are the main active components (Zha et al., 2012). Treatment with polysaccharides from *L. japonica* could significantly reduce fasting blood glucose and increase the levels of insulin and/or amylin in diabetic mice model (Li, Yu, Long, Guo, & Duan, 2012; Jia, Yang, Wang, Liu, & Xie, 2014). High fiber intake from dried whole seaweed supplements which consist of *L. japonica* and *Undaria pinnatifida* (48 g/day) could significantly reduce the concentrations of fasting and postprandial blood glucose and favorably altered lipid levels in 20 obese diabetic individuals after a intervention of 4 weeks (Kim, Kim, Choi, & Lee, 2008). The above findings indicate that *Laminaria* has rich antidiabetic potential, but further investigations are required to reveal the mechanisms associated with improving diabetic parameters, such as fasting and postprandial blood glucose concentrations.

2.4 *Sargassum* C.Agardh

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily of ligand-activated transcription factors (Michalik et al., 2006). There are three isotypes of PPAR, i.e. PPARα, PPARβ/δ (PPARδ) and PPARγ (Gervois, Fruchart & Staels, 2007). Particularly, PPARα and PPARγ are regarded as important pharmacological targets for the therapy of dyslipidemia and insulin-resistant diabetes, respectively (Pershadsingh, 2006). PPARγ has been demonstrated to be the major functional receptor for the thiazolidinedione

class of insulin-sensitizing drugs (Spiegelman, 1998). Activation of PPARα, which is predominantly expressed in the liver, could stimulate lipid consumption by enhancing the expression of fatty acid oxidation genes (Harrity et al., 2006). Combination the action of PPARα with PPARγ (PPARα/γ) are supposed to ameliorate both dyslipidemia and insulin sensitivity. Sargaquinoic acid (**9**) and sargahydroquinoic acid (**10**), extracted from *Sargassum yezoense* (Yamada) Yoshida & T.Konno, were identified as novel PPARα/γ dual agonists (Kim, 2008). Sargaquinoic acid (**9**) and sargahydroquinoic acid (**10**) have beneficial effects on glucose and lipid metabolism to improve metabolic disorders through dual activation of PPARα/γ transcriptional activities without showing severe adverse effects as observed with previously identified PPAR agonists (e.g., body weight gain, heart failure, renal failure, urinary cancer and anemia) (Adeghate, Adem, Hasan, Tekes, & Kalasz, 2011; Kim, Lee, Bae, & Kee 2012).

Sargassum ringgoldianum Harvey and *S. hemiphyllum* (Turner) C.Agardh extracts have high concentration of polyphenols and fucoxanthin (**11**), respectively. Both of them possess α-glucosidase and α-amylase inhibitory activities as well as property of insulin secretion stimulation (Lee & Han, 2012; Hwang, Hung, Tsai, Chien, & Kong, 2014). Fucoidans are complex and heterogeneous sulphated polysaccharides that usually found in brown macroalgae, such as *Fucus vesiculosus*, *Ecklonia kurome*, and *Undaria pinnatifida*. Fucoidans extracted from *S. wightii* Greville ex J.Agardh could inhibit α-glucosidase (Vinoth et al., 2015). Thunberol (**12**), a sterol from the Chinese brown macroalga *S. thunbergii* (Mertens ex Roth) Kuntze, which is one of prolific seaweed growing widely along the coast of East China Sea, has been reported to inhibit the activity of PTP1B significantly with an IC_{50} value of 2.24 mg/mL (He, Yao, Liu, & Guo, 2014). An *in vivo* study revealed that a supplement of the *S. coreanum* J. Agardh extract could lower the blood glucose concentration by regulating the hepatic glucose metabolic enzyme activities and improving insulin resistance (Park, Nam, & Han, 2015). *S. polycystum* C. Agardh contains various nutrients and is traditionally used against several human diseases (Motshakeri et al., 2014). Both the alcohol and the water extracts of *S. polycystum* could obviously reduce the levels of blood glucose and hemoglobin A1c (HbA1c) by increasing the response to insulin (Motshakeri, Ebrahimi, Goh, Matanjun, & Mohamed, 2013). HbA1c was incorporated into the diagnostic

criteria for diabetes in updated 2010 guidelines of the American Diabetes Association (ADA, 2010; WHO, 2011). The genus *Sargassum* has a wide range of active substances, but only limited studies have been performed on their antidiabetic activity.

2.5 Others

Eisenia bicyclis (Kijillman) Setchell (Lessoniaceae) is a perennial and daily consumed edible brown alga that inhabits the middle Pacific coastlines of Korea and Japan. Phloroglucinol derivatives isolated from *E. bicyclis* exhibited great potential for the effective therapy of diabetic complications by inhibiting advanced glycation end-products (AGEs) formation and α-amylase activity (Okada, Ishimaru, Suzuki, & Okuyama, 2004). *E. bicyclis* and *U. pinnatifida* (Harvey) Suringar high levels of fucoxanthin (**11**) and was shown to display potent inhibitory activity against AGEs formation and human recombinant aldose reductase (HRAR), rat lens aldose reductase (RLAR) and PTP1B activity (Ah et al., 2012). Phlorotannins extracted from *Fucus vesiculosus* L. (Fucaceae) inhibited the formation of AGEs mediated by glucose and methylglyoxal in a concentration-dependent manner (Liu & Gu, 2012). AGEs are the result of the Maillard reaction (nonenzymatic reaction), and may be formed as a result of normal metabolism and aging (Bakker et al., 2015). The accumulation of AGEs plays a pivotal role in the development and progression of diabetic complications (Rigalleau et al., 2015). Therefore, it may provide a potential means to control the development of diabetic complications by inhibiting AGEs formation.

Fucoxanthin (**11**), a marine carotenoid that is characteristically present in edible brown macroalgaes such as *E. bicyclis* (Arame), *U. pinnatifida* (Wakame), was reported to improve insulin resistance and to ameliorate blood glucose levels (D'Orazio et al., 2012; Maeda & Dominguez, 2013). Insulin resistance is an important pathophysiological mechanism that predicts the progression to type 2 diabetes. Also, an *in vivo* study on high fat diet-induced obesity mice reflected that the fucoxanthin-rich diet could significantly suppress the body weight and white adipose tissue weight gain induced by the high fat diet and promoted mRNA expression of glucose transporter 4 (GLUT4) mRNA in skeletal muscle tissues (Maeda, Hosokawa, Sashima, Murakami-Funayama, & Miyashita, 2009). The glucose uptake in surrounding tissues is mediated by GLUT4 translocation which stimulated by Akt

(Ramachandran & Saravanan, 2015). Increasing the expression of GLUT4 could improve insulin sensitivity, thus reducing or preventing insulin resistance. Fucosterol (**1**) constitutes 83–97% of the sterol content in brown macroalgae, and fucosterol (**1**) from *Eisenia bicyclis* and *Ecklonia stolonifera* was found to be a promising candidate for the treatment of diabetes and diabetic complications through inhibiting HRAR, RLAR, PTP1B, α-glucosidase activities and AGEs formation (Jung et al., 2013; Sánchez-Machado, López-Hernández, Paseiro-Losada, & López-Cervantes, 2004). Fucoidans derived from the *Sporophyll* of *Undaria pinnatifida* were reported to substantially prevent hyperglycemia based on oral glucose tolerance tests in non-diabetic mice and significantly reduced the levels of blood glucose in diabetic mice (Kim, Yoon, & Lee, 2012).

Ascophyllum nodosum (L.) Le Jolis is a dominant rocky intertidal brown macroalga that grows abundantly in the northeastern coast of North America and the northwestern coast of Europe (Taylor, 1957). Water extracts of *A. nodosum* exhibited strong inhibitory activity against α-glucosidase and its phenolic compounds could be implicated to this activity (Apostolidis, Karayannakidis, Kwon, Chong, & Seeram, 2011). Several other studies have also demonstrated that polyphenol-enriched extracts from *A. nodosum* could inhibit α-glucosidase and α-amylase *in vitro* as well as have the potential to influence glycemic control *in vivo* (Apostolidis & Lee, 2010; Kim, Rioux, & Turgeon, 2014; Pantidos, Boath, Lund, Conner, & McDougall, 2014). Both *Fucus vesiculosus* and *A. nodosum* contain large amounts of fucoidan. Interestingly, fucoidan extracted from *A. nodosum* has shown stronger inhibitory activity of α-glucosidase than that of extracted from *F. vesiculosus*. In contrast, fucoidan from *A. nodosum* decreased α-amylase activity but fucoidan extracted from *F. vesiculosus* did not (Kim, Rioux, & Turgeon, 2014). This finding suggests that the ability of fucoidan for inhibition of α-glucosidase and α-amylase varies due to different the algae species and harvest period. Also, a double-blind experiment on healthy adults reflected that a single ingestion of dried whole seaweed extract from *A. nodosum* and *F. vesiculosis* favorably regulated insulin levels and sensitivity after a carbohydrate-rich meal but displayed no significant effect on postprandial glucose response (Paradis, Couture, & Lamarche, 2011). Their potential benefits in diabetes management should be further investigated.

Ishige okamurae Yendo is as an edible brown alga that grows on rocks in the upper and

middle intertidal zone on rough open coasts, and generally forms highly persistent populations in clear waters (Zou et al., 2008). Diphlorethohydroxycarmalol (**13**), a kind of phlorotannin, isolated from *I. okamurae*, displayed prominent inhibitory effect against α-amylase and α-glucosidase that might provide a good way to the regulation of carbon source, such as starch, during fermentation (Heo et al., 2009). The extracts of *I. okamurae* were also shown to have the abilities to lower the blood glucose levels by regulating the activities of hepatic glucose metabolic enzymes and improving insulin resistance in db/db mice (Min, Kim, Jeon, & Han, 2011). Octaphlorethol A (OPA, **14**), a type of phlorotannin isolated from *I. foliacea* has been shown to have the potential to improve type 2 diabetes for the first time (Lee, Ko, Kang, Lee, & Jeon, 2016). The OPA significantly improved fasting blood glucose level and impaired glucose tolerance in type 2 diabetic db/db mice with the mechanism of increasing in GLUT4-mediated glucose utilization via activation of AMPK in muscle.

Overall, there is a huge knowledge gap exists between Phaeophyta bioactive compounds and their roles in antidiabetic activities. Brown algae are rich in bioactive substances and many *in vitro* studies have demonstrated the hypoglycemic potential of many of those compounds. However, further research using *in vivo* studies should be conducted to offer a better understanding of the potential mechanisms of those compounds.

3. Rhodophyta (red algae)

There are some red macroalgae that contain the bromophenols as algal enzyme inhibitors linked to diabetes mellitus (Table 2), such as the family Rhodomelaceae. *Grateloupia elliptica* Holmes contain two bromophenols such as 2,4,6-tribromophenol (**15**) and 2,4-dibromophenol (**16**) with α-glucosidase inhibitory activity (Kim, Nam, Kurihara, & Kim, 2008; Kurihara, Mitani, Kawabata, & Takahashi, 1999b). Bromophenol extracts of *G. elliptica* can inhibit intestinal α-glucosidase and stimulated basal glucose uptake into 3T3-L1 adipocytes (Kim, Nam, Kurihara, & Kim, 2008). Five highly brominated metabolites compounds (**17–21**; Table 2) isolated from a Chinese red alga *Laurencia similis* showed inhibitory activities against PTP1B (Qin et al., 2010). The compound named bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**22**) was purified from *Odonthalia corymbifera*

and *Polyopes lancifolia* possessed strong activity against α-glucosidases. Meanwhile, six bromophenols (**23–28**; Table 2) isolated from the Japanese red alga *O. corymbifera* also showed α-glucosidase inhibitory activity (Kurihara et al., 1999a). The two bromophenols such as 3-bromo-4,5-dihydroxybenzyl alcohol (**29**) and 3-bromo-4,5-dihydroxybenzyl methyl ether (**30**) from *Polysiphonia morrowii* displayed activity against α-glucosidase were identified for the first time from this species (Kurihara et al., 1999b). Bis-(2,3-dibromo-4,5-dihydroxyphenyl)-methane (**31**), isolated from red macroalgae *Rhodomela confervoides* (Hudson) P.C.Silva showed significant inhibition against PTP1B (Li, Guo, Su, Han, & Shi, 2008). What's more, an *in vivo* study also demonstrated the antihyperglycemic effect of bromophenols (Shi et al., 2008). Four bromophenols namely 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)-1,2-benzene-diol (**32**), 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(isopropoxymethyl)benzyl)benzene-1,2-diol (**33**), 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetra-hydroxydiphenyl methane (**34**) and 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxy-methyldiphenyl methane (**35**) are all bromophenols isolated from *Rhodomela confervoides* which have potent PTP1B inhibition (Jiang, Shi, Cui, & Guo, 2012; Shi et al., 2008; Shi, 2013). A series of bromophenols (**36–43**) purified from red alga *Symphylocladia latiuscula* exhibited antidiabetic activity by inhibiting PTP1B. Otherwise, Kurihara et al. (1999a) have reported a bromophenol 2,3,6-tribromo-4,5-dihydroxybenzyl alcohol (**44**) isolated from *S. latiuscula* wtih α-glucosidase inhibition at a very low concentration.

Among the red seaweeds, *Hypnea musciformis* (Wulfen) J.V.Lamouroux extract diplayed antihyperglycemic, antioxidant and increased plasma insulin effects in diabetic animals (Anandakumar, Balamurugan, Rajadurai, & Vani, 2008). The edible red alga *Gelidium amansii* (J.V. Lamouroux) J.V. Lamouroux is mainly distributed in northeastern Taiwan. A mice study has shown that the plasma glucose significantly decreased in the group with oral treatment of *G. amansii* ethanol extract (Choi et al., 2015). The plasma glucose, triglyceride, and cholesterol concentrations in rats with diabetes fed the *G. amansii* diet for 11-week were lower than of in rats with diabetes fed the control diet (Yang, Yao, & Chiang, 2015). *Gracilaria lemaneiformis* (Bory) Greville occurs widely in the marine environment and belongs to the family Gracilariaceae (Rhodophyta), and the sulfated polysaccharide accounts

for about 30% of its dry weight (Yu, Wang, Chen, Zhang, & Long, 2006). A polysaccharide extracted from *G. lemaneiformis* inhibited α-glucosidase activity *in vitro* and the administration of polysaccharide (200 mg/kg body weight) for 21 days significantly decreased the blood glucose levels in diabetic mice (Liao et al., 2015).

The extract of *Kappaphycus alvarezii* (Doty) Doty ex Silva and the ethanol extract of fresh *Eucheuma denticulatum* (N. L. Burman) Collins & Hervey demonstrated the appreciable inhibitory activities towards α-amylase (Balasubramaniam et al., 2013; Nagarani & Kamaguru, 2013). *K. alvarezii*, *K. striatus* (F. Schmitz) Doty ex P.C.Silva and *E. denticulatum* are good sources of magnesium, which could provide 30%–90% of the daily demand per 100 g of dried macroalgae (Balasubramaniam et al., 2013). It is highly plausible that magnesium in red macroalgae is responsible for hypoglycaemic activity. Intracellular free magnesium levels have been found to be closely and inversely related to the level of the fasting blood glucose (Barbagallo et al., 2003). Magnesium , one of the most abundant ions present in living cells, plays a pivotal role in insulin homeostasis and glucose metabolism through multiple enzymatic reactions and its plasma concentration is remarkably constant in endocrine (Barbagallo et al., 2003). It was shown that serum magnesium levels declined with rise in HbA1c levels and with duration of type 2 diabetes (Ramadass, Basu, & Srinivasan, 2015). Thus, increased consumption of magnesium-rich macroalgae may reduce the risk of type 2 diabetes. Gyeongshingangjeehwan 18 (GGEx18) is a kind of herbal drug composed of three medicinal plants: *Rheum palmatum* L. (Polygonaceae), *Laminaria japonica* Aresch (Laminariaceae), and *Ephedra sinica* Stapf (Ephedraceae). A study revealed that GGEx18 could significantly increase the expression of fatty acid oxidation genes, such as adiponectin, AMPKs, PPARα and its target enzymes, and CPT-1, in both mesenteric adipose tissues and 3T3-L1 cells and normalized hyperglycemia and hyperinsulinemia in obese mice, thus reduce the blood glucose levels (Oh et al., 2014). Porphyran from the red alga *Porphyra yezoensis* Ueda is a water-soluble dietary fiber. A study revealed that dietary porphyran should increase adiponectin levels thus improving glucose metabolism in diabetes (Kitano et al., 2012). Adiponectin is an adipokine that exerts a strong insulin-sensitizing effect by binding to its receptors like AdipoR1 and AdipoR2, resulting in activation of AMPK, PPARα, and presumably some other unknown signaling pathways (Kadowaki et al., 2006). Therefore, the

adiponectin gene appears to be a promising candidate susceptibility gene for type 2 diabetes.

Most of the seaweeds contain high contents of soluble dietary fibers such as carrageenan, agar, and alginates, which could passively retard digestion and glucose absorption. The beneficial effects of *Rhodophyta* species on the prevention and management of diabetes-related risks have clearly been indicated from *in vitro* and *in vivo* animal models. Nevertheless, deep and systematic studies, especiallyfocusing on mechanisms of action, are still needed. Studies on *Rhodophyta* sp. and *Rhodophyta*-derived compounds with hypoglycemic activity are still insufficient. Thus, further research in this area is imperative to look for more species with hypoglycemic activity and to provide strong evidence of potential beneficial effects of hypoglycemic functional foods or drugs from macroalgae.

4. Chlorophyta (green algae)

Ulva lactuca L. is a common green macroalga in the division Chlorophyta and found widespread in China (Tian, Yin, Zeng, Zhu, & Chen, 2015). Polysaccharides isolated from *U. lactuca* could significantly decrease the blood glucose by their potential inhibitory effect on key enzymes closely related to starch digestion and absorption in both plasma and small intestine (Belhadj, Hentati, Elfeki, & Hamden, 2013). The *Ulva rigida* ethanolic extract decreased blood glucose concentrations and micronuclei frequency in diabetic rats (Celikler et al., 2009; Tas, Celikler, Ziyanok- Ayvalik, Sarandol, & Dirican, 2011). Oxidative stress is an important factor which responsible for complications in diabetes (Sukmawati et al., 2015). Diabetes is generally accompanied by increased production of the molecules of reactive oxygen species and/or impaired antioxidant defense systems, which lead to oxidative damage to biomolecules. Exposure of the genetic material to reactive oxygen species could cause DNA damage (Evans, Dizdaroglu, & Cooke, 2004). There are some reports on the antidiabetic activities of other *Ulva* species, such as *U. fasciata* Delile, have the abilities to reduce blood glucose level, and restore hepatic glycogen content, carbohydrate metablic enzymes like hexokinase, glusokinase and glucose 6-phoshatase activity *in vivo* (Abirami & Kowsalya, 2013). Protein kinase C is a family of protein kinase enzymes that are involved in controlling the intracellular signal transduction (Anderson, Mcgill, & Tuttle, 2007). The activation of protein kinase C may occur in the organs susceptible to developing diabetic

complications, especially diabetic nephropathy (Kizub, Klymenko, & Soloviev, 2014).

5. Potential anti-diabetic natural products from marine algae

The WHO Expert Committee recommended that medicinal plants used in the treatment of diabetes be further investigated as they are frequently considered to be lesser or no adverse effects (Halberstein, 2005). Search for more safe and effective bioactive agents has continued to be an important target in the field of diabetic research. Less than 1% of the estimated 250,000 higher plants have been screened pharmacologically and very few in regard to diabetes (Arumugam, Manjula, & Paari, 2013). The ethnobotanical information reports state that about 800 plants and their active extracts which may possess hypoglycemic potential have been found. In which, about 200 pure bioactive compounds have been identified and reported for their potential anti-diabetic effects (Alarcon-Aguilara et al., 1998; Suksomboon, Poolsup, Boonkaew, & Suthisisang, 2011). These natural phytoconstituents showing anti-diabetic efficacy include flavonoids, alkaloids, tannins, saponins, terpenoids, phenolics, glycosides, steroids, chalcones, carotenoids, peptides, lipids, glycopeptides, iridoids, ursolic acid and imidazoline (Wu, Hsieh, Lin, & Yen, 2013). The bioactive compounds are found in many fruits, vegetables, herbs, tea, soy and beverage products, and mostly together responsible for efficacy (Edirisinghe & Burton-Freeman, 2016).

So far, approximately 22,000 natural products of marine organisms have been discovered whereas 131,000 terrestrial natural products exist (Blunt, Copp, Munro, Northcote, & Prinsep, 2011). According to a recent study, an estimate of 72,500 algal species has been described throughout the world, where as most of them are marine (Guiry, 2012). To survive in various diverse and extreme environments, marine macroalgae produce a variety of natural bioactive compounds and metabolites (Wang, Li, Lee, & Chang, 2017). Polyphenols and polysaccharides from marine macroalgae particularly showed very significant antidiabetic potential against pharmacological experimental systems via interfering in carbohydrate metabolism. Marine algae-derived functional metabolites indicate structural and functional diversity from their terrestrial counter-part due to the differences in their metabolic pathways (Guven, Percot, & Sezik, 2010). Algal polyphenols are derived from polymerized phloroglucinol units, whereas polyphenols from terrestrial plants are derived from gallic and

ellagic acids. They are termed as phlorotannins and biosynthesized via acetate malonate pathway (Arnold & Targett, 2002). At all events, the most active candidates will be determined through measuring different biochemical parameters such as fasting blood glucose, insulin, glycosylated hemoglobin, lipid profile, serum urea and creatinine, plasma alanine and aspartate transaminases, or microscopical examinations of pancreatic sections.

6. Conclusion

Marine macroalgae and functional ingredients derived from them have increasingly been playing a more and more important role in body health and human nutrition. Bioactive constituents from marine macroalgae and their byproducts, like phlorotannins, fucosterol, and carotenoid pigments including fucoxanthin can be used indirectly as functional ingredients for the reduction of incidences of many chronic diseases in humans (Li & Kim, 2011). Diabetes mellitus has been considered to be one of the most important global health problems and there are many potential ways for macroalgae and macroalgae-derived bioactive compounds to treat diabetes, including α-glucosidase and α-amylase inhibition, activation of both AMPK and Akt signal pathways as well as HRAR, RLAR, PTP1B activities and AGE formation inhibition etc. Marine macroalgae are usually perceived as less toxic with fewer side-effects compared with those synthetic antidiabetic drugs. Current understanding on the antidiabetic effects of marine macroalgae and their compounds is almost based on the data available from *in vitro* and *in vivo* animal studies, however, these data cannot be extrapolated into the human setting without reliable human clinical data. Further investigations are imperative to unveil many more macroalgae and their components, which may have antidiabetic potentials. It is also important to look in to the possible mechanisms of antidiabetic actions of these marine macroalgae and their compounds. These antidiabetic therapeutics from natural source are valuable lead compounds, However, they seldom can be for direct clinical use and structural modifications are necessary. As a primary requirement for drug development, the future potential of algal natural products used in diabetes will be based on the modification of structures of biologically active compounds. In addition, original alga-derived natural products is unfeasible to meet market demands and alternative resupply approaches are being developed based on biotechnological production or chemical

semi-synthesis from naturally occurring precursors. Industry-scale production of complex natural products can be harvested in the future align with the progress of the knowledge of plant biosynthetic pathways and the development of more efficient genetic engineering strategies and tools. It is of immense importance to gain idea on enhancement of bioavailability and intrinsic potency with structure–activity relationship studies of algal bioactive compounds for the treatment of diabetes. Moreover, clinical research is needed to confirm the real efficacy of marine macroalgae to aid in diabetes prevention and management . Pharmacists should encourage patients to seek advice about the addition of these antidiabetic therapeutics for the treatment of diabetes. More research is needed to identify and quantify the phytochemical compounds on diabetes, as well as the combination therapy of algal natural products with the synthetic drugs. It is reasonable to state that marine macroalgae seem to have great developing potential in medicinal preparation to be sustainable nutraceutical or functional foods for complementary and alternative diabetes therapy.

Acknowledgement

This work was financially supported by Fujian Province Key Laboratory for the Development of Bioactive Material from Marine Algae grant (2017FZSK05), Natural Science Foundation (2016J06009) and Marine High-tech Industrial Development Project (MIN2014-17) of Fujian Province, China. The project was also supported by and by the FAFU grants KXb16011A and 612014043.

References

Abirami, R. G., & Kowsalya, S. (2013). Antidiabetic activity of *Ulva fasciata* and its impact on carbohydrate metabol-ism enzymes in alloxan induced diabetic rats. *International Journal of Pharmacognosy and Phytochemical Research, 3*, 136–141.

ADA. (2005). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 28*, S37–S42.

ADA. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes care, 33*, S62–S69.

ADA. (2015). Classification and diagnosis of diabetes. *Diabetes Care, 40*, S11–S24.

Adeghate, E., Adem, A., Hasan, M. Y., Tekes, K., & Kalasz, H. (2011). Medicinal chemistry

and actions of dual and pan PPAR modulators. *The Open Medicinal Chemistry Journal, 5*, 93–98.

Ah, J. H., Nurul, I. M., Mee, L. C., Oh, J. H., Young, C. H., Chul, W. H., et al. (2012). Promising antidiabetic potential of fucoxanthin isolated from the edible brown algae *Eisenia bicyclis* and *Undaria pinnatifida*. *Fisheries Science, 78*, 1321–1329.

Alarcon-Aguilara, F. J., Roman-Ramos, R., Perez-Gutierrez, S., Aguilar-Contreras, A., Contreras-Weber, C. C., & Flores-Saenz, J. L. (1998). Study of the antihyperglycemic effect of plants used as antidiabetics. *Journal of Ethnopharmacology*, *61*, 101–110.

Anandakumar, S., Balamurugan M., Rajadurai, M., & Vani B. (2008). Antihyperglycemic and antioxidant effects of red algae *Hypnea musciformis* in alloxan-induced diabetic rats. *Biomedicine*, *28*, 34–38.

Anderson, P. W., Mcgill, J. B., & Tuttle, K. R. (2007). Protein kinase C β inhibition: the promise for treatment of diabetic nephropathy. *Current Opinion in Nephrology and Hypertension, 16*, 397–402.

Apostolidis, E., & Lee, C. (2010). *In vitro* potential of *Ascophyllum nodosum* phenolic antioxidant- mediated α- glucosidase and α- amylase inhibition. *Journal of Food Science, 75*, H97–H102.

Apostolidis, E., Karayannakidis, P. D., Kwon, Y. I., Chong, M. L., & Seeram, N. P. (2011). Seasonal variation of phenolic antioxidant-mediated α-glucosidase inhibition of *Ascophyllum nodosum*. *Plant Foods for Human Nutrition, 66*, 313–319.

Arnold, T. M., & Targett, N. M. (2002). Marine tannins: The importance of a mechanistic framework for predicting ecological roles. *Journal of Chemical Ecology*, *28*, 1919–1934.

Arumugam, G., Manjula, P., & Paari N. (2013). A review: Anti diabetic medicinal plants used for diabetes mellitus. *Journal of Acute Disease*, 196–200.

Atlas, I. D. (2009). The global burden. International Diabetes Federation. 4th Edition Brussels, 21–27.

Bakker, S. F., Tushuizen, M. E., Gözütok, E., Çiftci, A., Gelderman, K. A., Mulder, C. J., et al. (2015). Advanced glycation end products (AGEs) and the soluble receptor for AGE (sRAGE) in patients with type 1 diabetes and coeliac disease. *Nutrition, Metabolism and*

Cardiovascular Diseases, *25*, 230–235.

Balasubramaniam, V., Mustar, S., Khalid, N. M., Rashed, A. A., Noh, M. F. M., Wilcox, M. D., et al. (2013). Inhibitory activities of three Malaysian edible seaweeds on lipase and α-amylase. *Journal of Applied Phycology*, *25*, 1405–1412.

Barbagallo, M., Dominguez, L. J., Galioto, A., Ferlisi, A., Cani, C., Malfa, L., et al. (2003). Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. *Molecular Aspects of Medicine, 24*, 39–52.

Belhadj, S., Hentati, O., Elfeki, A., & Hamden, K. (2013). Inhibitory activities of *Ulva lactuca* polysaccharides on digestive enzymes related to diabetes and obesity. *Archives of Physiology and Biochemistry, 119*, 81–87.

Bijland, S., Mancini, S. J., & Salt, I. P. (2013). Role of AMP-activated protein kinase in adipose tissue metabolism and inflammation. *Clinical Science, 124*, 491–507.

Blunt, J. W., Copp, B. R., Munro, M. H. G., Northcote, P. T., & Prinsep, M. R. (2011). Marine natural products. *Natural Product Reports*, *28*, 196–268.

Bu, T., Liu, M., Zheng, L., Guo, Y., & Lin, X. (2010). α-glucosidase inhibition and the *in vivo* hypoglycemic effect of butyl-isobutyl-phthalate derived from the *Laminaria japonica* rhizoid. *Phytotherapy Research*, *24*, 1588–1591

Celikler, S., Tas, S., Vatan, O., Ziyanok-Ayvalik, S., Yildiz, G., & Bilaloglu, R. (2009). Anti-hyperglycemic and antigenotoxic potential of *Ulva rigida* ethanolic extract in the experimental diabetes mellitus. *Food and Chemical Toxicology*, *47*, 1837–1840.

Choi, S., Oh, H., Jung, J., Park, S., Park, Y. I., Bak, S., & Lee, M. (2015). Effect of agar-free *Gelidium amansii* on obesity in DIO C57BL/6J mice model. *The FASEB Journal, 29*, S750.2.

Choochote, W., Suklampoo, L., & Ochaikul, D. (2014). Evaluation of antioxidant capacities of green microalgae. *Journal of Applied Phycology*, *26*, 43–48.

Cicirelli, M. F., Tonks, N. K., Diltz, C. D., Weiel, J. E., Fischer, E. H., & Krebs, E. (1990). Microinjection of a protein-tyrosine-phosphatase inhibits insulin action in *Xenopus* oocytes. *Proceedings of the National Academy of Sciences*, *87*, 5514–5518.

D'Orazio, N., Gemello, E., Gammone, M. A., de Girolamo, M., Ficoneri, C., & Riccioni, G. (2012). Fucoxantin: A treasure from the sea. *Marine Drugs*, *10*, 604–616.

Edirisinghe, I., & Burton-Freeman, B. (2016). Anti-diabetic actions of Berry polyphenols – Review on proposed mechanisms of action. *Journal of Berry Research*, *6*, 237–250.

Elchebly, M., Payette, P., Michaliszyn, E., Cromlish, W., Collins, S., Loy, A. L., et al. (1999). Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. *Science, 283*, 1544–1548.

Evans, M. D., Dizdaroglu, M., & Cooke, M. S. (2004). Oxidative DNA damage and disease: induction, repair and significance. *Mutation Research/Reviews in Mutation Research*, *567*, 1–61.

Gervois, P., Fruchart, J. C., & Staels, B. (2007). Drug Insight: mechanisms of action and therapeutic applications for agonists of peroxisome proliferator-activated receptors. *Nature Clinical Practice Endocrinology and Metabolism*, *3*, 145–156.

Gouveia, L., Nobre, B. P., Marcelo, F. M., Mrejen, S., Cardoso, M. T., Palavra, A. F., et al. (2007). Functional food oil coloured by pigments extracted from microalgae with supercritical CO_2. *Food Chemistry*, *101*, 717–723.

Guiry, M. D. (2012). How many species of algae are there? *Journal of Phycology*, *48*, 1057–1063.

Gupta, S., & Abu-Ghannam, N. (2011). Bioactive potential and possible health effects of edible brown seaweeds. *Trends in Food Science and Technology*, *22*, 315–326.

Guven, K. C., Percot, A., & Sezik, E. (2010). Alkaloids in marine algae. *Marine Drugs*, *8*, 269–284.

Halberstein, R. A. (2005). Medicinal plants: historical and cross-cultural usage patterns. *Annals of Epidemiology*, *15*, 686–699.

Hardie, D. (2008). AMPK: a key regulator of energy balance in the single cell and the whole organism. *International Journal of Obesity, 32*, S7–S12.

Harrity, T., Farrelly, D., Tieman, A., Chu, C., Kunselman, L., Gu, L., et al. (2006). Muraglitazar, a novel dual (alpha/gamma) peroxisome proliferator-activated receptor activator, improves diabetes and other metabolic abnormalities and preserves beta-cell function in db/db mice. *Diabetes, 55*, 240–248.

He, W. F., Yao, L. G., Liu, H. L., & Guo, Y. W. (2014). Thunberol, a new sterol from the Chinese brown alga *Sargassum thunbergii*. *Journal of Asian Natural Products Research*,

16, 685–689.

Heo, S. J., Hwang, J. Y., Choi, J. I., Han, J. S., Kim, H. J., & Jeon, Y. J. (2009). Diphlorethohydroxycarmalol isolated from *Ishige okamurae*, a brown algae, a potent α-glucosidase and α-amylase inhibitor, alleviates postprandial hyperglycemia in diabetic mice. *European Journal of Pharmacology*, *615*, 252–256.

Hwang, P. A., Hung, Y. L., Tsai, Y. K., Chien, S. Y., & Kong, Z. L. (2014). The brown seaweed *Sargassum hemiphyllum* exhibits α-amylase and α-glucosidase inhibitory activity and enhances insulin release *in vitro*. *Cytotechnology*, *67*, 653–660.

Iwai, K. (2008). Antidiabetic and antioxidant effects of polyphenols in brown alga *Ecklonia stolonifera* in genetically diabetic KK-Ay mice. *Plant Foods for Human Nutrition, 63*(4), 163–169.

Jia, X., Yang, J., Wang, Z., Liu, R., & Xie, R. (2014). Polysaccharides from *Laminaria japonica* show hypoglycemic and hypolipidemic activities in mice with experimentally induced diabetes. *Experimental Biology and Medicine*, *239*, 1663–1670.

Jiang, B., Shi, D., Cui, Y., & Guo, S. (2012). Design, synthesis, and biological evaluation of bromophenol derivatives as protein tyrosine phosphatase 1B inhibitors. *Archiv Der Pharmazie*, *345*, 444–453.

Jung, H. A., Islam, M. N., Lee, C. M., Oh, S. H., Lee, S., Jung, J. H., et al. (2013). Kinetics and molecular docking studies of an anti-diabetic complication inhibitor fucosterol from edible brown algae *Eisenia bicyclis* and *Ecklonia stolonifera*. *Chemico-Biological Interactions*, *206*, 55–62.

Jung, M., Park, M., Lee, H. C., Kang, Y. H., Kang, E. S., & Kim, S. K. (2006). Antidiabetic agents from medicinal plants. *Current Medicinal Chemistry*, *13*, 1203–1218.

Kadowaki, T., Yamauchi, T., Kubota, N., Hara, K., Ueki, K., & Tobe, K. (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *Journal of Clinical Investigation, 116*, 1784–1792.

Kandra, L. (2003). α-Amylases of medical and industrial importance. *Journal of Molecular Structure Theochem*, 487–498.

Kang, C., Jin, Y. B., Lee, H., Cha, M., Sohn, E. T., Moon, J., et al. (2010). Brown alga *Ecklonia cava* attenuates type 1 diabetes by activating AMPK and Akt signaling

pathways. *Food and Chemical Toxicology*, *48*, 509–516.

Kang, M. C., Wijesinghe, W. A. J. P., Lee, S. H., Kang, S. M., Ko, S. C., Yang, X., et al. (2012). Dieckol isolated from brown seaweed *Ecklonia cava* attenuates type II diabetes in db/db mouse model. *Food and Chemical Toxicology An International Journal Published for the British Industrial Biological Research Association*, *53*, 294.

Khan, W., Rayirath, U. P., Subramanian, S., Jithesh, M. N., Rayorath, P., Hodges, D. M., et al. (2009). Seaweed extracts as biostimulants of plant growth and development. *Journal of Plant Growth Regulation*, *28*, 386–399.

Kim, K. J., Yoon, K. Y., & Lee, B. Y. (2012). Fucoidan regulate blood glucose homeostasis in C57BL/KSJ m+/+ *db* and C57BL/KSJ *db*/*db* mice. *Fitoterapia*, *83*, 1105–1109.

Kim, K. T., Rioux, L. E., & Turgeon, S. L. (2014). Alpha-amylase and alpha-glucosidase inhibition is differentially modulated by fucoidan obtained from *Fucus vesiculosus* and *Ascophyllum nodosum*. *Phytochemistry*, *98*, 27–33.

Kim, K. Y., Kurihara, H., & Kim, S. M. (2010). α-Glucosidase inhibitory activity of bromophenol purified from the red alga *Polyopes lancifolia*. *Journal of Food Science, 75*, H145–H150.

Kim, K., Nam, K., Kurihara, H., & Kim, S. (2008). Potent α-glucosidase inhibitors purified from the red alga *Grateloupia elliptica*. *Phytochemistry*, *69*, 2820–2825.

Kim, M. S., Kim, J. Y., Choi, W. H., & Lee, S. S. (2008). Effects of seaweed supplementation on blood glucose concentration, lipid profile, and antioxidant enzyme activities in patients with type 2 diabetes mellitus. *Nutrition Research and Practice*, *2*, 62–67.

Kim, S. N. (2008). Sargaquinoic acid and sargahydroquinoic acid from *Sargassum yezoense* stimulate adipocyte differentiation through PPAR alpha/gamma activation in 3T3-L1 cells. *FEBS Letters*, *582*, 3465–3472.

Kim, S. N., Lee, W., Bae, G. U., & Kee, Y. K. (2012). Anti-diabetic and hypolipidemic effects of *Sargassum yezoense* in *db/db* mice. *Biochemical and Biophysical Research Communications*, *424*, 675–680.

Kitano, Y., Murazumi, K., Duan, J., Kurose, K., Kobayashi, S., Sugawara, T., et al. (2012). Effect of dietary porphyran from the red alga, *Porphyra yezoensis*, on glucose metabolism in diabetic KK-Ay mice. *Journal of Nutritional Science and Vitaminology*,

58, 14–19.

Kizub, I. V., Klymenko, K. I., & Soloviev, A. I. (2014). Protein kinase C in enhanced vascular tone in diabetes mellitus. *International Journal of Cardiology*, *174*, 230–242.

Kurihara, H., Mitani, T., Kawabata, J., & Takahashi, K. (1999a). Two new bromophenols from the red alga Odonthalia corymbifera. *Journal of Natural Products*, *62*, 882–884.

Kurihara, H., Mitani, T., Kawabata, J., & Takahashi, K. (1999b). Inhibitory potencies of bromophenols from *Rhodomelaceae algae* against α-glucosidase activity. *Fisheries Science*, *65*, 300–303.

Lee, C. W., & Han, J. S. (2012). Hypoglycemic effect of *Sargassum ringgoldianum* extract in STZ-induced diabetic mice. *Preventive Nutrition and Food Science*, *17*, 8–13.

Lee, S. (2003). Anti-oxidant activities of fucosterol from the marine algae *Pelvetia siliquosa*. *Archives of Pharmacal Research*, *26*, 719–722.

Lee, S. H., & Jeon, Y. J. (2013). Anti-diabetic effects of brown algae derived phlorotannins, marine polyphenols through diverse mechanisms. *Fitoterapia*, *86*, 129–136.

Lee, S. H., Kang, N., Kim, E. A., Heo, S. J., Moon, S. H., Jeon, B. T., et al. (2014). Antidiabetogenic and antioxidative effects of octaphlorethol a isolated from the brown algae *Ishige foliacea* in streptozotocin-induced diabetic mice. *Food Science and Biotechnology*, *23*, 1261–1266.

Lee, S. H., Karadeniz, F., Kim, M. M., & Kim, S. K. (2009). α- Glucosidase and α- amylase inhibitory activities of phloroglucinal derivatives from edible marine brown alga, *Ecklonia cava*. *Journal of the Science of Food and Agriculture*, *89*, 1552–1558.

Lee, S. H., Ko, S. C., Kang, M. C., Lee, D. H., & Jeon, Y. J. (2016). Octaphlorethol a, a marine algae product, exhibits antidiabetic effects in type 2 diabetic mice by activating amp-activated protein kinase and upregulating the expression of glucose transporter 4. *Food and Chemical Toxicology*, *91*, 58–64.

Lee, S. H., Min, K. H., Han, J. S., Lee, D. H., Park, D. B., Jung, W. K., et al. (2012). Effects of brown alga, *Ecklonia cava* on glucose and lipid metabolism in C57BL/KsJ- d*b*/*db* mice, a model of type 2 diabetes mellitus. *Food and Chemical Toxicology*, *50*, 575–582.

Lee, S. H., Park, M. H., Heo, S. J., Kang, S. M., Ko, S. C., Han, J. S., et al. (2010). Dieckol isolated from *Ecklonia cava* inhibits α-glucosidase and α-amylase *in vitro* and alleviates

postprandial hyperglycemia in streptozotocin-induced diabetic mice. *Food and Chemical Toxicology*, *48*, 2633–2637.

Lee, S. H., Ko, S. C., Kang, M. C., Lee, D. H., Jeon, Y. J. (2016). Octaphlorethol A, a marine algae product, exhibits antidiabetic effects in type 2 diabetic mice by activating AMP-activated protein kinase and upregulating the expression of glucose transporter 4. *Food and Chemical Toxicology*, 91, 58-64.

Lee, Y. S., Shin, K. H., Kim, B. K., & Lee, S. (2004). Anti-diabetic activities of fucosterol from *Pelvetia siliquosa*. *Archives of Pharmacal Research*, *27*, 1120–1122.

Li, J., Guo, S. J., Su, H., Han, L. J., & Shi, D. Y. (2008). Total synthesis of bis-(2,3-dibromo-4,5-dihydroxyphenyl)-methane as potent PTP1B inhibitor. *Chinese Chemical Letters*, *19*, 1290–1292.

Li, X. C, Niu, R. L., Fan, X., Han, L. J., & Zhang, L. X. (2005). Macroalage as a source of alpha-glucosidase inhibitors. *Chinese Journal of Oceanology and Limnology*, *23*, 354–356.

Li, X., Yu, Z., Long, S., Guo, Y., & Duan, D. (2012). Hypoglycemic effect of *Laminaria japonica* polysaccharide in a type 2 diabetes mellitus mouse model. *Isrn Endocrinology*, *2012*, 507462.

Li, Y. X., & Kim, S. K. (2011). Utilization of seaweed derived ingredients as potential antioxidants and functional ingredients in the food industry: An overview. *Food Science and Biotechnology*, *20*, 1461–1466.

Liao, X., Yang, L., Chen, M., Yu, J., Zhang, S., & Ju, Y. (2015). The hypoglycemic effect of a polysaccharide (GLP) from *Gracilaria lemaneiformis* and its degradation products in diabetic mice. *Food and Function*, *6*, 2542–2549.

Liu, H., & Gu, L. (2012). Phlorotannins from brown algae (*Fucus vesiculosus*) inhibited the formation of advanced glycation endproducts by scavenging reactive carbonyls. *Journal of Agricultural and Food Chemistry*, *60*, 1326–1334.

Liu, M., Zhang, W., Qiu, L., & Lin, X. K. (2011). Synthesis of butyl-isobutyl-phthalate and its interaction with α-glucosidase *in vitro*. *Journal of Biochemistry*, *149*, 27–33.

Liu, M., Zhang, W., Wei, J. T., & Lin, X. K. (2011). Synthesis and α-glucosidase inhibitory mechanisms of bis (2,3-dibromo-4,5-dihydroxybenzyl) ether, a potential marine

bromophenol α-glucosidase inhibitor. *Marine Drugs*, *9*, 1554–1565.

Liu, X., Li, X., Gao, L., Cui, C., Li, C., Li, J., et al. (2011). Extraction and PTP1B inhibitory activity of bromophenols from the marine red alga *Symphyocladia latiuscula*. *Chinese Journal of Oceanology and Limnolog*, *29*, 686–690.

Long, Y. C., & Zierath, J. R. (2006). AMP-activated protein kinase signaling in metabolic regulation. *Journal of Clinical Investigation*, *116*, 1776.

Maeda, H., & Dominguez, H. (2013). Anti-obesity and anti-diabetic activities of algae. *Functional Ingredients from Algae for Foods and Nutraceuticals*, *256*, 453–476.

Maeda, H., Hosokawa, M., Sashima, T., Murakami-Funayama, K., & Miyashita, K. (2009). Anti-obesity and anti-diabetic effects of fucoxanthin on diet-induced obesity conditions in a murine model. *Molecular Medicine Reports*, *2*, 897–902.

Manikkam, V., Vasiljevic, T., Donkor, O. N., Mathai, M. L. (2016). A review of potential marine-derived hypotensive and anti-obesity peptides. Critical Reviews in Food Science and Nutrition, 56, 92-112.

Michalik, L., Auwerx, J., Berger, J. P., Chatterjee, V. K., Glass, C. K., Gonzalez, F. J., et al. (2006). International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. *Pharmacological Reviews*, *58*, 726–741.

Min, K. H., Kim, H. J., Jeon, Y. J., & Han, J. S. (2011). Ishige okamurae ameliorates hyperglycemia and insulin resistance in C57BL/KsJ- *db/db* mice. *Diabetes Research and Clinical Practice*, *93*, 70–76.

Mohamed, S., Hashim, S. N., & Rahman, H. A. (2012). Seaweeds: A sustainable functional food for complementary and alternative therapy. *Trends in Food Science and Technology*, *23*, 83–96.

Moon, H. E., Islam, M. N., Ahn, B. R., Chowdhury, S. S., Sohn, H. S., Jung, H. A., et al. (2011). Protein tyrosine phosphatase 1B and α-glucosidase inhibitory phlorotannins from edible brown algae, *Ecklonia stolonifera* and *Eisenia bicyclis*. *Bioscience Biotechnology and Biochemistry*, *75*, 1472–1480.

Motshakeri, M., Ebrahimi, M., Goh, Y. M., Matanjun, P., & Mohamed, S. (2013). Sargassum polycystum reduces hyperglycaemia, dyslipidaemia and oxidative stress via increasing insulin sensitivity in a rat model of type 2 diabetes. *Journal of the Science of Food and*

Agriculture, *93*, 1772–1778.

Motshakeri, M., Ebrahimi, M., Goh, Y. M., Othman, H. H., Hair-Bejo, M., & Mohamed, S. (2014). Effects of brown seaweed (*Sargassum polycystum*) extracts on kidney, liver, and pancreas of type 2 diabetic rat model. *Evidence-based Complementary and Alternative Medicine: eCAM, 2014*, 68–78.

Nagarani, N., & Kamaguru, A. (2013). Evaluation of anti-inflammatory, antidiabetic, cytotoxic activity of *Kappaphycus alvarezii*. *International Journal of Pharma and Bio Sciences*, *4*, 921–929.

Oh, J., Lee, H., Lim, H., Woo, S., Shin, S. S., & Yoon, M. (2014). The herbal composition GGEx18 from *Laminaria japonica*, *Rheum palmatum*, and *Ephedra sinica* inhibits visceral obesity and insulin resistance by upregulating visceral adipose genes involved in fatty acid oxidation. *Pharmaceutical Biology*, *53*, 301–312.

Ohta, T., Sasaki, S., Oohori, T., Yoshikawa, S., & Kurihara, H. (2002). α-Glucosidase inhibitory activity of a 70% methanol extract from *Ezoishige* (*Pelvetia babingtonii* de Toni) and its effect on the elevation of blood glucose level in rats. *Bioscience, Biotechnology, and Biochemistry*, *66*, 1552–1554.

Okada, Y., Ishimaru, A., Suzuki, R., & Okuyama, T. (2004). A new phloroglucinol derivative from the brown alga *Eisenia bicyclis*: Potential for the effective treatment of diabetic complications. *Journal of Natural Products*, *67*, 103–105.

Padmalayam, I., & Suto, M. (2013). Role of adiponectin in the metabolic syndrome: current perspectives on its modulation as a treatment strategy. *Current Pharmaceutical Design*, *19*, 5755–5763.

Pangestuti, R., & Kim, S. K. (2011). Biological activities and health benefit effects of natural pigments derived from marine algae. *Journal of Functional Foods*, *3*, 255–266.

Pantidos, N., Boath, A., Lund, V., Conner, S., & McDougall, G. J. (2014). Phenolic-rich extracts from the edible seaweed, ascophyllum nodosum, inhibit α-amylase and α-glucosidase: Potential anti-hyperglycemic effects. *Journal of Functional Foods*, *10*, 201–209.

Paradis, M. E., Couture, P., & Lamarche, B. (2011). A randomised crossover placebo-controlled trial investigating the effect of brown seaweed (*Ascophyllum*

nodosum and *Fucus vesiculosus*) on postchallenge plasma glucose and insulin levels in men and women. *Applied Physiology, Nutrition, and Metabolism*, *36*, 913–919.

Park, M. H., Nam, Y. H., & Han, J. S. (2015). Sargassum coreanum extract alleviates hyperglycemia and improves insulin resistance in *db/db* diabetic mice. *Nutrition Research and Practice*, *9*, 472–479.

Pershadsingh, H. A. (2006). Dual peroxisome proliferator-activated receptor-α/γ agonists. *Treatments in Endocrinology*, *5*, 89-99.

Pontiroli, A. E. (2004). Type 2 diabetes mellitus is becoming the most common type of diabetes in school children. *Acta Diabetologica*, *41*, 85–90.

Qin, J., Su, H., Zhang, Y., Gao, J., Zhu, L., Wu, X., et al. (2010). Highly brominated metabolites frommarine red alga *Laurencia similis* inhibit protein tyrosine phosphatase 1B. *Bioorganic and Medicinal Chemistry Letters*, *20*, 7152–7154.

Ramachandran, V., & Saravanan, R. (2015). Glucose uptake through translocation and activation of GLUT4 in PI3K/Akt signaling pathway by asiatic acid in diabetic rats. *Human and Experimental Toxicology*, *34*, 884–893.

Ramadass, S., Basu, S., & Srinivasan, A. (2015). SERUM magnesium levels as an indicator of status of Diabetes Mellitus type 2. *Diabetes & Metabolic Syndrome: Clinical Research and Reviews*, *9*, 42–45.

Rengasamy, K. R., Kulkarni, M. G., Stirk, W. A., Van Staden, J. (2014). Advances in algal drug research with emphasis on enzyme inhibitors. *Biotechnology Advances*, *32*, 1364–1381.

Renner, S., & Ricklefs, E. (1995). Dioecy and its correlates in the flowering plants. *American Journal of Botany*, *82*, 596–606.

Rigalleau, V., Cougnard-Gregoire, A., Nov, S., Gonzalez, C., Maury, E., Lorrain, S., et al. (2015). Association of advanced glycation end products and chronic kidney disease with macroangiopathy in type 2 diabetes. *Journal of Diabetes and Its Complications, 29*, 270–274.

Roglic, G., Unwin, N., Bennett, P. H., Mathers, C., Tuomilehto, J., Nag, S., et al. (2005). The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care*, *28*, 2130–2135.

Ruocco, N., Costantini, S., Guariniello, S., Costantini, M. (2016). Polysaccharides from the marine environment with pharmacological, cosmeceutical and nutraceutical potential. *Molecules*, 21, 551.

Sánchez-Machado, D. I., López-Hernández, J., Paseiro-Losada, P., & López-Cervantes, J. (2004). An HPLC method for the quantification of sterols in edible seaweeds. *Biomedical Chromatography*, *18*, 183–190.

Saleh, A. S. M., Zhang, Q., & Shen, Q. (2016). Recent research in antihypertensive activity of food protein-derived hydrolyzates and peptides. *Critical Reviews in Food Science and Nutrition*, 56, 760-787.

Shi, D. (2013). HPN, a synthetic analogue of bromophenol from red alga *Rhodomela confervoides*: Synthesis and anti-diabetic effects in C57BL/KsJ-*db/db* mice. *Marine Drugs*, *11*, 350–362.

Shi, D. Y., Xu, F., He, J., Li, J., Xiao, F., & Han, L. J. (2008). Inhibition of bromophenols against PTP1B and anti-hyperglycemic effect of *Rhodomela confervoides* extract in diabetic rats. *Chineseence Bulletin*, *53*, 2476–2479.

Shirosaki, M., & Koyama, T. (2011). *Laminaria japonica* as a food for the prevention of obesity and diabetes. *Advances in Food and Nutrition Research*, *64*, 199–212.

Spiegelman, B. M. (1998). PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. *Diabetes*, *47*, 507–514.

Suleria, H. Á. R., Gobe, G., Masci, P., Osborne, S. A. (2016). Marine bioactive compounds and health promoting perspectives; innovation pathways for drug discovery. *Trends in Food Science & Technology*, 50, 44-55.

Sukmawati, D., Fujimura, S., Jitsukawa, S., Ito-Hirano, R., Ishii, T., Sato, T., et al. (2015). Oxidative stress tolerance of early stage diabetic endothelial progenitor cell. *Regenerative Therapy*, *1*, 38–44.

Suksomboon, N., Poolsup, N., Boonkaew, S., & Suthisisang, C. C. (2011). Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes. *Journal of Ethnopharmacology*, *137*, 1328–1333.

Tas, S., Celikler, S., Ziyanok- Ayvalik, S., Sarandol, E., & Dirican, M. (2011). *Ulva rigida* improves carbohydrate metabolism, hyperlipidemia and oxidative stress in

streptozotocin- induced diabetic rats. *Cell Biochemistry and Function*, *29*, 108–113.

Taylor, W. R. (1957). Book reviews: marine algae of the northeastern coast of north america. *Science*, 126.

Thilagam, E., Parimaladevi, B., Kumarappan, C., Mandal, S. C. (2013). α-Glucosidase and α-amylase inhibitory activity of *Senna surattensis*. *Journal of Acupuncture and Meridian Studies*, *6*, 24–30.

Tian, H., Yin, X., Zeng, Q., Zhu, L., & Chen, J. (2015). Isolation, structure, and surfactant properties of polysaccharides from *Ulva lactuca* L. from South China Sea. *International Journal of Biological Macromolecules*, *79*, 577–582.

Vinayagam, R., Xiao, J.B., & Xu, B.J. (2017). An insight into anti-diabetic properties of dietary phytochemicals. *Phytochemistry Reviews*, *16*, 535–553.

Vinoth, K. T., Lakshmanasenthil, S., Geetharamani, D., Marudhupandi, T., Suja, G., & Suganya, P. (2015). Fucoidan: A α-D-glucosidase inhibitor from *Sargassum wightii* with relevance to type 2 diabetes mellitus therapy. *International Journal of Biological Macromolecules*, *72C*, 1044–1047.

Wälchli, S., Curchod, M. L., Gobert, R. P., Arkinstall, S., & van Huijsduijnen, R. H. (2000). Identification of *Tyrosine Phosphatases* that dephosphorylate the insulin receptor a Brute Force approch based on "Substrate-Trapping" mutants. *Journal of Biological Chemistry*, *275*, 9792–9796.

Wang, H. D., Li, X. C., Lee D. J., & Chang J. S. (2017). Potential biomedical applications of marine algae. *Bioresource Technology*, http://dx.doi.org/10.1016/j.biortech.2017.05.198.

WHO. (2011). Use of glycated haemoglobin (HbA1c) in diagnosis of diabetes mellitus: abbreviated report of a WHO consultation.

Wu, C. H., Hsieh, H. T., Lin, J. A., & Yen, G. C. (2013). Alternanthera paronychioides protects pancreatic β-cells from glucotoxicity by its antioxidant, antiapoptotic and insulin secretagogue actions. *Food Chemistry*, *139*, 362–370.

Xiao, J. B., Högger P. (2015). Dietary polyphenols and type 2 diabetes: current insights and future perspectives. *Current Medicinal Chemistry*, 22, 23–38.

Xu, H. L., Kitajim, C., Ito, H., Miyazaki, T., Bab, M., Okuyam, T., & Ok, Y. (2012). Antidiabetic effect of polyphenols from brown alga *Ecklonia kurome* in genetically

diabetic KK-Ay mice. *Pharmaceutical Biology*, *50*, 393–400.

Yang, T. H., Yao, H. T., & Chiang, M. T. (2015). Red algae (*Gelidium amansii*) reduces adiposity via activation of lipolysis in rats with diabetes induced by streptozotocin-nicotinamide. *Journal of Food and Drug Analysis*, *23*, 758–765.

Yoon, J. S., Yadunandam, A. K., Kim, S. J., Woo, H. C., Kim, H. R., & Kim, G. D. (2013). Dieckol, isolated from *Ecklonia stolonifera*, induces apoptosis in human hepatocellular carcinoma Hep3B cells. *Journal of Natural Medicines*, *67*, 519–527.

Yotsu-Yamashita, M., Kondo, S., Segawa, S., Lin, Y. C., Toyohara, H., Ito, H., et al. (2013). Isolation and structural determination of two novel phlorotannins from the brown alga *Ecklonia kurome* Okamura, and their radical scavenging activities. *Marine Drugs*, *11*, 165–183.

Yu, J., Wang, X., Chen, M. Z., Zhang, Y. Y., & Long, Z. J. (2006). Analysis on nutritional components and polysaccharide composition of gracilaria lemaneiformis from Chaoshan Coast. *Food Science*, *27*, 93–97.

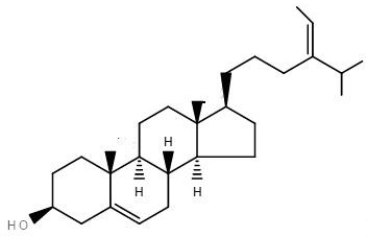
Zha, X. Q., Xiao, J. J., Zhang, H. N., Wang, J. H., Pan, L. H., Yang, X. F., et al. (2012). Polysaccharides in *Laminaria japonica* (LP): Extraction, physicochemical properties and their hypolipidemic activities in diet-induced mouse model of atherosclerosis. *Food Chemistry*, *134*, 244–252.

Zhang, S., & Zhang, Z. Y. (2007). PTP1B as a drug target: recent developments in PTP1B inhibitor discovery. *Drug Discovery Today*, *12*, 373–381.

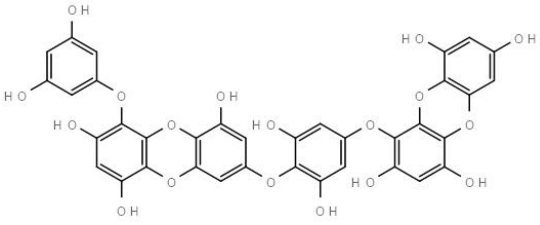
Zhao, C., Wu, Y. J., Yang, C. F., Liu, B., & Huang, Y, F. (2015). Hypotensive, hypoglycemic and hypolipidemic effects of bioactive compounds from microalgae and marine microorganisms. *International Journal of Food Science and Technology*, *50*, 1705–1717.

Zou, Y., Qian, Z. J., Li, Y., Kim, M. M., Lee, S. H., & Kim, S. K. (2008). Antioxidant effects of phlorotannins isolated from *Ishige okamurae* in free radical mediated oxidative systems. *Journal of Agricultural and Food Chemistry*, *56*, 7001–7009.

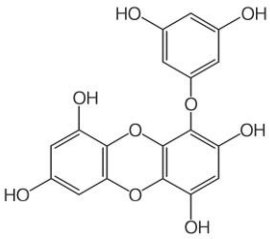
Fig. 1 Chemical structures of bioactive compounds from marine macroalgae (references seen in Table 1 and Table 2)



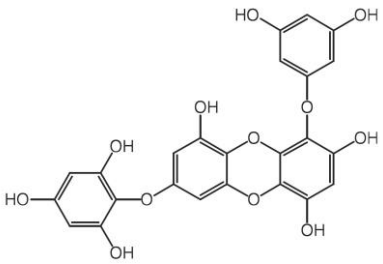
1 *Fucosterol*



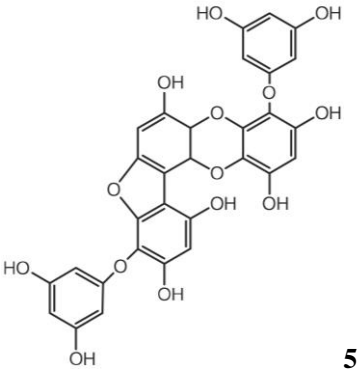
2 *Dieckol*



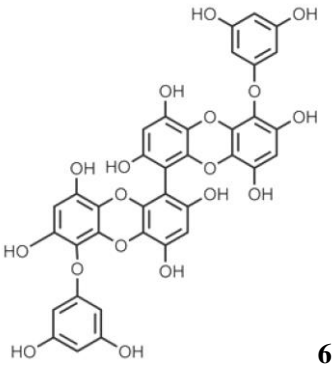
3 *Eckol*



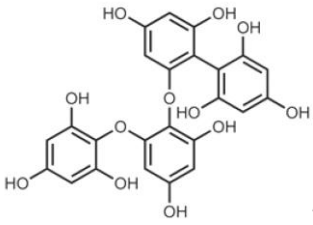
4 *7-Phloroeckol*



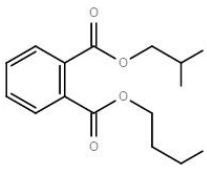
5 *Phlorofucofuroeckol-A*



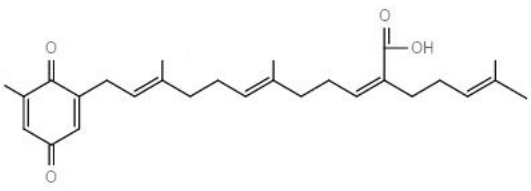
6 *6,6-Bieckol*

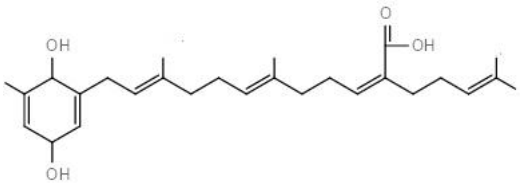


7 *Fucodiphloroethol-G*

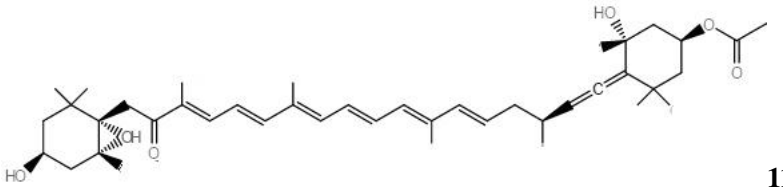


8 *Butyl-isobutyl-phthalate*

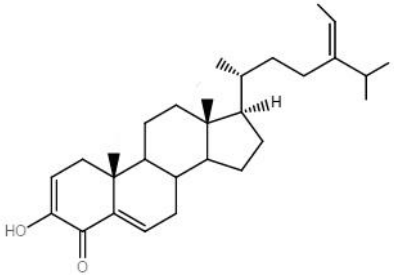


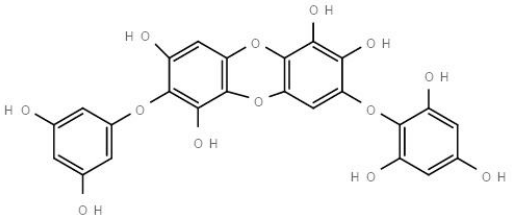


9 *Sargaquinoic acid* **10** *Sargahydroquinoic acid*

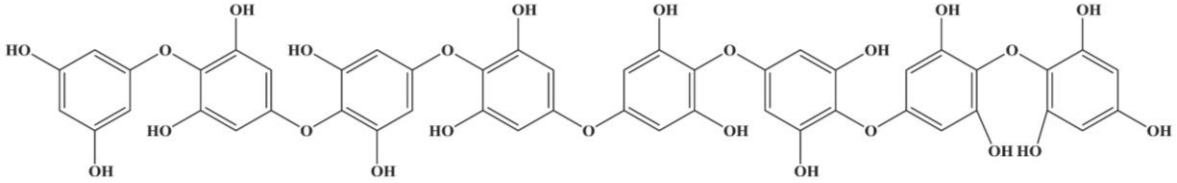


11 *Fucoxanthin*

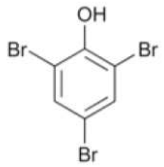


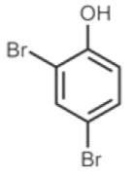


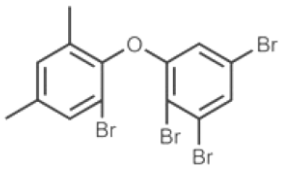
12 *Thunberol* **13** *Diphlorethohydroxycarmalol*



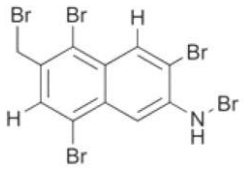
14 *Octaphlorethol A*

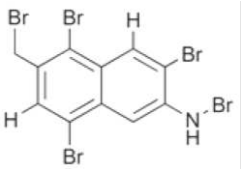


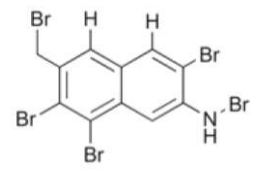


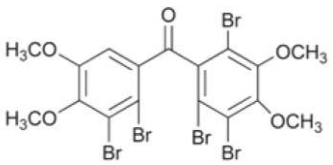


15 *2,4,6-Tribromophenol* **16** *2,4- Dibromophenol* **17** *3',5',6',6-Tetrabromo-2,4-dimethyldiphenyl ether*

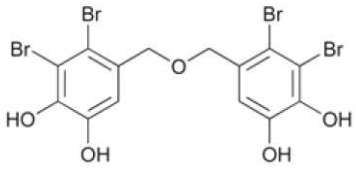




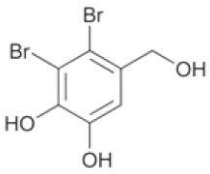




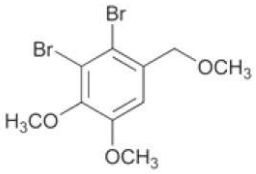
18 **19** **20** **21**



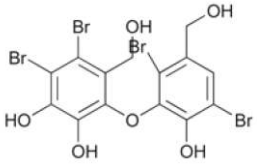
22



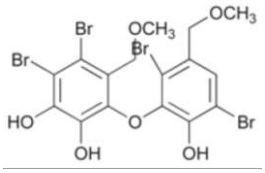
23



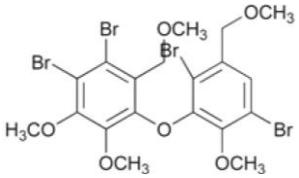
24



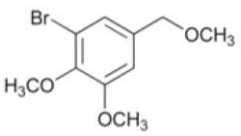
25



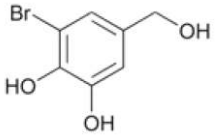
26



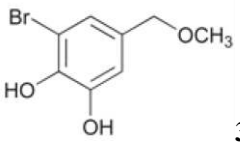
27



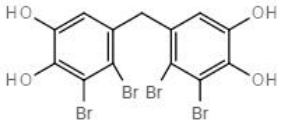
28



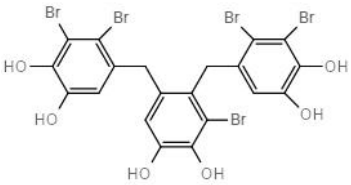
29



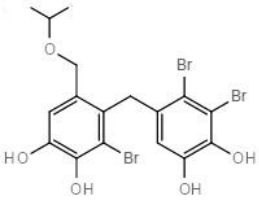
30



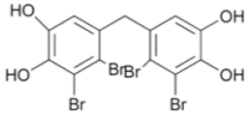
31



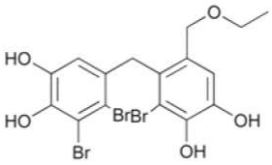
32



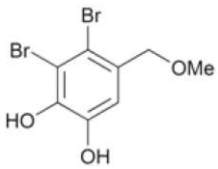
33



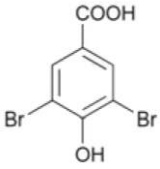
34



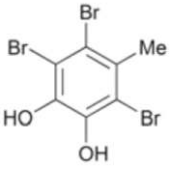
35



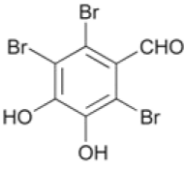
36



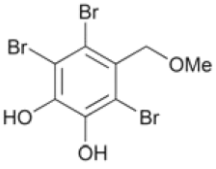
37



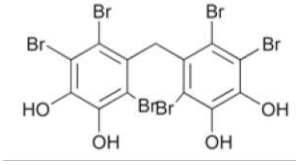
38



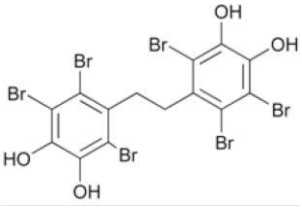
39



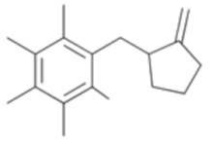
40



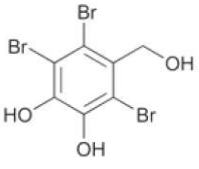
41



42



43



44

Fig. 1

Table 1 Preclinical trials with marine macroalgae

Macroalgae	Major compound	Effects	References
Pelvetia siliquosa	Fucosterol (**1**)	Inhibition of blood glucose level and glycogen degradation	Lee et al., 2004
Pelvetia babingtonii	Methanol extract	α-Glucosidase inhibition and suppression of postprandial hyperglycemia	Ohta et al., 2002
Ecklonia stolonifera	Polyphenols	α-Glucosidase inhibition; Suppression of the increase in plasma glucose	Gouveia et al., 2007; Iwai, 2008
	Phlorotannins	PTP1B and α-glucosidase inhibition	Moon et al., 2011
	Fucosterol (**1**)	RLAR, HRAR, PTP1B, α-glucosidase activities and AGE formation inhibition	Jung et al., 2013
Eisenia bicyclis	Dieckol (**2**)	α-Glucosidase and PTP1B	Moon et al., 2011
Ecklonia stolonifera	Eckol (**3**)		
	7-Phloroeckol (**4**)		
	Phlorofucofuroeckol-A (**5**)		
Ecklonia cava	Dieckol (**2**)	Activation of both AMPK and Akt signal pathways; Improvement of insulin sensitivity; α-Glucosidase and α-amylase inhibition	Kang et al., 2012
	7-Phloroeckol (**4**)		Pontiroli, 2004
	Phlorofucofuroeckol-A (**5**)		Lee et al., 2010
	6,6-Bieckol (**6**)		
	Fucodiphloroethol-G (**7**)		
Ecklonia kurome	Phlorotannins	α-Amylase inhibition; Amelioration of hyperinsulinemia	Xu et al., 2012
Laminaria japonica	Polysaccharides	Reduced fasting blood glucose; Increased the levels of insulin and amylin	Li et al., 2012; Jia et al., 2014
	Butyl-isobutyl-phthalate (**8**)	α-Glucosidase inhibition	Bu et al. 2010
Sargassum ringgoldianum	Polyphenol	α-Amylase and α-glucosidase inhibition	Lee et al., 2012
Sargassum yezoense	Sargaquinoic acid (**9**)	Enhances the transcriptional activities of PPARα and PPARγ	Kim et al., 2012
	Sargahydroquinoic acid (**10**)	Amelioration of insulin resistance	Kim, 2008
Sargassum wightii	Fucoidan	α-D-glucosidase inhibition	Vinoth et al., 2015
Sargassum polycystum	Extract	Increasing insulin sensitivity	Motshakeri et al., 2013
Sargassum hemiphyllum	Fucoxanthin (**11**)	α-Amylase, α-glucosidase inhibition and insulin release enhancement	Hwang et al., 2014
Sargassum thunbergii	Thunberol (**12**)	PTP1B inhibition	He, Yao, Liu, & Guo, 2014
Sargassum coreanum	Extract	Alteration of the hepatic glucose metabolic enzyme activities and improvement of	Park, Nam, & Han, 2015

		insulin resistance	
Undaria pinnatifida	Fucoxanthin (**11**)	HRAR, RLAR, PTP1B inhibition, and AGE formation	Ah et al., 2012
		Improve insulin signaling	Maeda et al., 2013
Eisenia bicyclis	Phlorotannins	Inhibition of AGEs and α-amylase	Okada et al., 2004
	Fucoxanthin (**11**)	Inhibition of RLAR, HRAR, PTP1B activities and AGE formation	Ah et al., 2012
	Fucosterol (**1**)	Inhibition of RLAR, HRAR, PTP1B, α-glucosidase activities and AGE formation	Jung et al., 2013
Ascophyllum nodosum	Phlorotannins	α-Amylase and α-glucosidase inhibition	Apostolidis et al., 2011; Kim et al., 2014; Pantidos et al., 2014
	Fucoidan		
Ishige okamurae	Diphlorethohydroxycarmalol (**13**)	α-Amylase and α-glucosidase inhibition	Heo et al., 2009
Ishige okamurae	Extract	Altering the hepatic glucose metabolic enzyme activities and improves insulin resistance.	Min et al., 2011
Ishige foliacea	Octaphlorethol A (**14**)	Increasing in GLUT4-mediated glucose utilization via activation of AMPK in muscle.	Lee, Ko, Kang, Lee, & Jeon, 2016
Kappaphycus alvarezii	Extract	Inhibitory activity towards α-amylase	Nagarani & Kamaguru 2013; Balasubramaniam et al., 2013
Eucheuma denticulatum			
Gracilaria lemaneiformis	Polysaccharide	Inhibitory to the α-glucosidase activity; decrease in blood glucose levels	Liao et al., 2015
Gelidium amansiithe	Ethanol extract	Plasma glucose significantly decreased	Choi et al., 2015
Porphyra yezoensis	Porphyran	Increasing adiponectin levels	Kitano et al., 2012
Ulva rigida	Ethanolic extract	Regeneration of β-cells and/or potentiating the insulin release	Celikler et al., 2009; Tas et al., 2011
Ulva fasciata	Sulfated polysaccharides	Reduce blood glucose level, and restore hepatic glycogen content and carbohydrate metablic enzymes	Abirami & Kowsalya, 2013
Ulva lactuca	Polysaccharides	α-Amylase, maltase and sucrase inhibition; Delay glucose absorption	Belhadj et al., 2013

Table 2 The bromophenols from red algae as algal enzyme inhibitors linked to diabetes mellitus

Red algae	Bromophenols	Major activity	References
Grateloupia elliptica	2,4,6-Tribromophenol (**15**)	α-Glucosidase inhibition	Kim, Nam, Kurihara, & Kim, 2008
	2,4-Dibromophenol (**16**)		
Laurencia similis	3′,5′,6′,6-Tetrabromo-2,4-dimethyldiphenyl ether (**17**)	PTP1B inhibition	Qin et al., 2010
	1,2,5-Tribromo-3-bromoamino-7-bromomethylnaphthalene (**18**)		
	2,5,8-Tribromo-3-bromoamino-7-bromomethylnaphthalene (**19**)		
	2,5,6-Tribromo-3-bromoamino-7-bromomethylnaphthalene (**20**)		
	2′,5′,6′,5,6-Pentabromo-3′,4′,3,4-tetramethoxybenzo-phenone (**21**)		
	Bis-(2,3-dibromo-4,5-dihydroxybenzyl) ether (**22**)		
Odonthalia corymbifera	Bis-(2,3-dibromo-4,5-dihydroxybenzyl) ether (**22**)	α-Glucosidase inhibition	Kurihara et al., 1999a
	2,3-Dibromo-4,5-dihydroxybenzyl alcohol (**23**)		
	2,3-Dibromo-4,5-dimethoxybenzyl methyl ether (**24**)		
	4-Bromo-2,3-dihydroxy-6-hydroxymethylphenyl		
	2,5-dibromo-6-hydroxy-3-hydroxymethylphenyl ether (**25**)		
	4-Bromo-2,3-dimethoxy-6-methoxymethylphenyl		
	2,5-dibromo-6-methoxy-3-methoxymethylphenyl ether (**26**)		
	4-Bromo-2,3-dimethoxy-6-methoxymethylphenyl		
	2,5-dibromo-6-methoxy-3-methoxymethylphenyl ether (**27**)		
	3-Bromo-4,5-dimethoxybenzyl methyl ether (**28**)		
Polyopes lancifolia	Bis-(2,3-dibromo-4,5-dihydroxybenzyl) ether (**22**)	α-Glucosidase inhibition	Kim, Kurihara, & Kim, 2010
Polysiphonia morrowii	3-Bromo-4,5-dihydroxybenzyl alcohol (**29**)	α-Glucosidase inhibition	Kurihara et al., 1999b
	3-Bromo-4,5-dihydroxybenzyl methyl ether (**30**)		
Rhodomela confervoides	Bis-(2,3-dibromo-4,5-dihydroxybenzyl) methane (**31**)	Potent PTP1B inhibition	Li et al., 2008;
	3-Bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)-1,2-benzene-diol (**32**)		Jiang et al., 2012; Shi 2013
	3,4-Dibromo-5-(2-bromo-3,4-dihydroxy-6-(isopropoxymethyl)benzyl)benzene-1,2-diol (**33**)		

	2,2′,3,3′-Tetrabromo-4,4′,5,5′-tetra-hydroxydiphenyl methane (**34**)		Shi et al., 2008
	2,2′,3-Tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxy-methyldiphenyl methane (**35**)		
Symphylocladia latiuscula	2,3-Dibromo-4,5-dihydroxybenzyl methyl ether (**36**)	PTP1B inhibition	Liu et al., 2011
	3,5-Dibromo-4-hydroxybenzoic acid (**37**)		
	2,3,6-Tribromo-4,5-dihydroxymethylbenzene (**38**)		
	2,3,6-Tribromo-4,5-dihydroxybenzaldehyde (**39**)		
	2,3,6-Tribromo-4,5-dihydroxybenzyl methyl ether (**40**)		
	Bis-(2,3,6-tribromo-4,5-dihydroxyphenyl) methane (**41**)		
	1,2-Bis-(2,3,6-tribromo-4,5-dihydroxyphenyl)-ethane (**42**)		
	1-(2,3,6-Tribromo-4,5-dihydroxybenzyl)-pyrrolidin-2-one (**43**)		
	2,3,6-Tribromo-4,5-dihydroxybenzyl alcohol (**44**)	α-Glucosidase inhibition	Kurihara et al., 1999a