Marine Peptides Attenuate Oxidative Stress to Manage Diabetes And Diabetes- Related Parameters

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Abstract

An increasing prevalence of diabetes, in the last few decades, is known as a main risk for human health worldwide. Due to patience's inconvenience, unaffordability and adverse effects of synthetic drugs, a large number of diabetic patients are in search of alternative therapeutics while marine products have been placed at the top. Marine peptides, among all marine products, are highly impactful due to their bioactive properties as potential nutraceutical and effective therapeutics. Therefore, this review has focused on the marine bioactive products having antioxidative effects leading to attenuate diabetes and diabetes-related complications. The manuscript also tried to understand the underlying mechanism for antidiabetic actions showed by the marine products especially marine peptides. A systematic literature review has been undergone to collect the relevant data on the said issue using authentic portals for biological and medical journals which displayed marine peptides and their derivatives having high antidiabetic effects, commercial values, wider pharmaceutical and nutraceutical markets. Recent advances in the understanding of the effect of marine products explored their antioxidative potentials, regulation on glucose metabolism (including insulin-regulated glucose metabolism), enhancing glucose-stimulated insulin secretion and inhibition α-amylase activities. A large number of them are already in different phases of the clinical and preclinical pipeline. This review showcases the trends and prospects of marine products in the management of diabetes and diabetes-related complications for the future with special emphasis on mechanistic approach.

Keywords: Antidiabetic, Marine peptide, antioxidant, hydrolysate, collagen

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1. Introduction

Diabetes mellitus is one of the serious and chronic metabolic defects in insulin secretion and/or insulin action eventually leads to hyperglycemia and insulin resistance. Insulin resistance is a crucial factor in the development of type 2 diabetes mellitus (T2DM) and can result from high levels of free fatty acids (FFA) that inhibit glucose transportation (Bogan, 2012). The impaired insulin-secretion and glucose tolerance ultimately result developing T2DM (Belfort et al., 2005). FFAs can also inhibit the expression of coacivator-1 for peroxisome proliferator-activated receptors (PPARs), essential transcriptional regulators for adipogenesis, triglyceride (TG) synthesis and storage (Gelman et al., 2007). Activation of PPARs can mitigate lipotoxicity by inducing mitochondrial biogenesis, increasing FFA oxidation and downregulating low-grade inflammation (Guilherme et al., 2008). The deficiency in the PPAR-related signaling can interfere with the role of mitochondria in the muscle and liver leading to ectopic FFA worsening hyperglycemia. Long-term hyperglycemia and hyperlipidemia cause oxidative stress, chronic inflammation and advanced deposition of the glycation substances facilitating diabetic secondary complication development. Furthermore, the PPARs are the ideal therapeutic targets for the development of antidiabetic and antihypertensive drugs. Interestingly, dietary nutrients contain activators for PPARs which can regulate metabolic inflammation. While available medical therapies, along with rigorous diet, exercise and dietary supplements can effectively regulate the coexistence of hypertension and hyperglycemia (Meeuwisse-Pasterkamp et al., 2008). Therefore, development of new therapies to minimize the impact of diabetes and diabetes-related complications should be of great significance. Fortunately, the marine bioactive compounds constitute an enticing and promising pool of candidates for antidiabetic drugs. Previous researches have shown that marine peptides have bioactivity against growth of tumors, hypertension, hyperlipidemia and diabetes (Aneiros and Garateix, 2004).

Treatment with marine proteins improves insulin sensitivity in insulin-resistant individuals and reduces insulin-resistance-related metabolic disorders (Chiasson et al., 2003). In addition, marine collagen peptides (MCPs) from fish hydrolysate have been documented to inhibit angiotensin I-converting enzyme (ACE) activity which was evident for especially diabetic nephropathy (Qi et al., 2007). Previous studies have demonstrated that MCPs from deep sea fish can reduce hyperlipidemia, modulate immune function and have antioxidation activity in animal models (Pei et al., 2008). Accordingly, we hypothesized that MCPs might regulate glucose and lipid metabolism and thus benefit patients with T2DM, hypertension and other diabetes-related secondary complications. This review illustrates the prospects, dimensions and probable mechanism how the marine peptides contribute to manage diabetes and diabetes related parameters.

Graphical Abstract

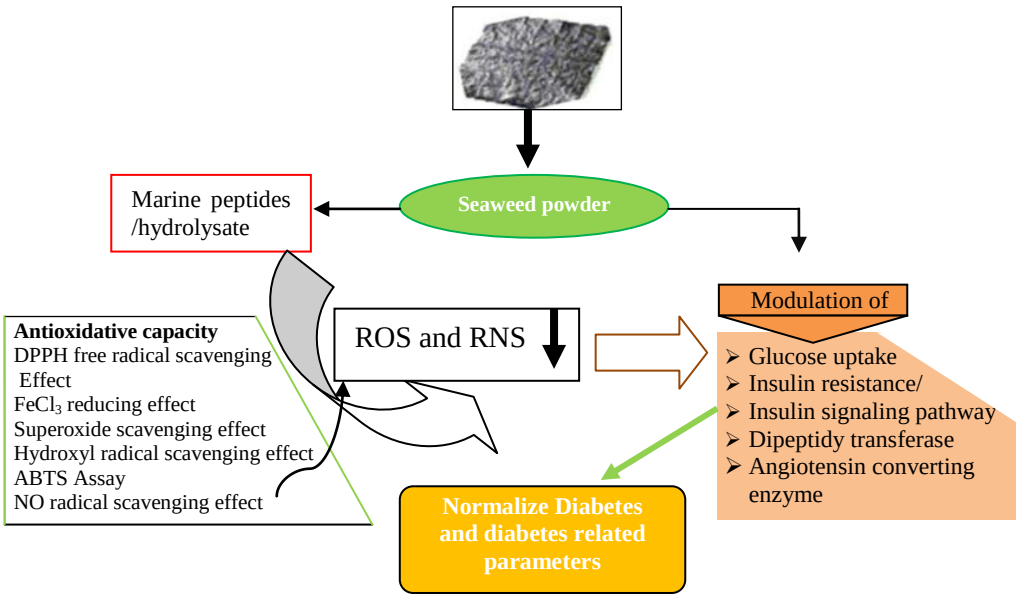

Figure 1 : Marine peptides/products regulate diabetes and diabetes related conditions

2. Materials and methods

Google scholar, Medline, Pubmed and Sciencedirect were used as prime search-hubs to gather major relevant scientific information. Some articles have been cited from other journals directly accessing to the web-site of those journals. Literatures published in recent years are preferred for appropriate behavior. Keyword combinations for the search were: marine algae, *marine peptides*, collagen peptides, diabetes, and type 2 diabetes management.

2.1 Marine peptides as anti-diabetic products

The oceans that form 90 percent of the biosphere covering about 70 percent of the Earth's surface. Marine ecosystems account for almost half of the global biodiversity and in recent decades they have been extensively explored for possible sources of novel bioactive natural products. In recent years, marine organism-based peptides have so far been extensively searched to discover their bioregulatory functions together with the mechanism of action as potential drugs for diabetes and diabetes-related parameters (Aneiros and Garateix, 2004). A few fish protein hydrolysates have shown *in vivo* glucose uptake-stimulating activity and could be used in hyperglycaemia management in addition to regular therapy. These glucose-stimulating hydrolysates can improve glucose tolerance either by stimulating glucose absorption or by increasing insulin sensitivity in target cells. Suppressed fasting blood levels of glycated hemoglobin A1c, leptin, insulin, total triglycerides, free fatty acids, total cholesterol, low density

lipoprotein-cholesterol, high sensitivity C-reactive protein and nitric oxide, but elevated levels of high density lipoprotein-cholesterol, insulin sensitivity index bradykinin, prostacycline, and adiponectin were observed in Chinese patients with type 2 diabetes mellitus following daily treatment with 13 g marine collagen peptides from fish hydrolysate for 1.5 and 3 months (Power et al., 2009). Treatment of T2DM with oligopeptides from marine salmon skin decreased blood glucose levels by reducing oxidative stress and inflammation, as evident by attenuated serum tumor necrosis factor-α, interferon gamma and malondialdehyde, but increased superoxide dismutase and glutathione peroxidase which exerted anti-apoptotic effect on pancreatic beta-cells activity (Horner et al., 2016).

2.2 Marine collagen-peptide (MCP), a functional food for diabetes

Marine collagen peptide, derived from fish-skin, bones and scales is used as a functional food or dietary supplement. Oral administration of collagen hydrolysates and glucagon-like-peptide (GLP) with GLP-1-dependent and GLP-1-independent system increase glucose tolerance in normal mice (Iba et al., 2016). Collagen molecules' polypeptide chains consist of several repeats of a tripeptide complex, Gly-X-Y, in which X and Y are respectively proline and hydroxyprolin. The Gly-Pro-Hyp tripeptide (10.5%) is highly represented to the various tripeptide units; the other tripeptides include Gly-Pro-Ala, Gly- Ala-Hyp and Gly-Leu-Hyp (3.4-5.5%) of which Gly-Pro-Ala is a known as dipeptidyl peptidase-4 (DPP-4) inhibitor (Bauvois, 1998). Collagen peptide with DPP-4 inhibition property has great relevance as a natural source for T2DM management via incretin effect. Using this ability, several *in vitro, in vivo* ((Li-Chan et al., 2012; Hsieh et al., 2015) and human clinical trials (Zhu et al., 2017) have been conducted on the hypoglycemic effect of collagen-derived peptides (Sugihara et al. 2015).

3. Marine products in diabetes regulations

3.1 Antioxidative role of marine products

Marine bioactive peptides from fish, algae, mollusk, crustacean, and marine by-products including substandard muscles, viscera, skins, trimmings and shell have an attractive and promising pool of drug candidates (Table 1) as important antioxidative agents (Kim and Wijesekara, 2010). Our previous studies have shown that MCP treatment in rats with T2DM induced by a high-fat diet can inhibit oxidative stress and protect β-cells in pancreatic islets (Lassoued et al., 2015). We also found that MCP supplements in Chinese patients with T2DM and hypertension can have beneficial effects on glucose and lipid metabolism, insulin sensitivity, renal function and hypertension control (Koehnk et al., 2015). In one of our studies, *Padina tenuis, a* marine alga has been found to show excellent antioxidative role in DPPH radical scavenging, ferric reducing, superoxide scavenging and iron chelating assays. The antidiabetic potential of *P. tenuis* has been summarized in **Table 2**. Kidney and pancreatic architecture of *P. tenuis* treated animals have also been improved (Figure 2) (Arabi et al., 2020). Hypothetically, low molecular weight peptides are thought to have

higher antioxidant ability due to their easier access to lipid radicals and affectivity to quench them than large peptides thus inhibiting the spread of lipid peroxidation through free radical means (Samaranayaka, et al., 2010).

Table 1. Antioxidant Peptides Derived from Marine Sources: Amino Acid Sequence and Methods Used in Measuring Antioxidant Activity.

Source	Amino acid sequence	Methods	Ref.
Prawn	IKK, FKK, and FIKK	Ferric thiocyanate method	Suetsuna, 2000
Microalgae	MPGPLSPL	DPPH, *OH and $O2^{\bullet -}$ - radical scavenging (ESR)	Ryu et al, 2012
Microalgae	VECYGPNRPQF	DPPH, *OH, $O2^{\bullet -}$ -, peroxyl and ABTS radical scavenging	Sheih et al, 2010
Squid	NGPLQAGQPGER and FDSGPAGVL	LAPS, metal chelation, *OH and R* radical scavenging (ESR)	Mendis et al., 2005
Oyster	LKQELEDLLEKQE	LAPS, *OH and $O2^{\bullet -}$ - radical scavenging (ESR)	Qian et al, 2008
Blue mussel	FGHPY	LAPS and *OH radical scavenging (ESR)	Jung et al., 2005
Horse mackerel	NHRYDR	DPPH and *OH radical scavenging (ESR)	Kumar et al, 2012
Croaker	GNRGFACRHA	DPPH and *OH radical scavenging (ESR)	Kumar et al, 2012
Yellowfin sole	RPDFDLEPPY	LAPS	Jun et al., 2004
Jellyfish	NLDTPYCFYSGDYGG	$O2^{\bullet -}$ - radical scavenging	Li et al., 2012
Bullfrog skin	LEELEEELEGCE	DPPH, *OH, $O2^{\bullet -}$ - and peroxyl radical scavenging (ESR)	Qian et al., 2008
Sphyrna lewini	WDR, PYFNK	ABTS, DPPH, *OH and $O2^{\bullet -}$ - radical scavenging	Wang et al., 2012
Tuna	LPTSEAAKY and PMDYMVT	DPPH and ferric thiocyanate method	Hsu, 2010
Marine algae	LNGDVW	DPPH, *OH and peroxyl radical scavenging (ESR)	Ko et al., 2012
Squid	NADFGLNGLEGLA and NGLEGLK	LAPS, *OH, $O2^{\bullet -}$ - and R* radical scavenging (ESR)	Rajapakse et a., 2005

Nasri et al. documented that orally-administered goby fish protein hydrolysates (not undigested) can potentially attenuate hyperglycemia and restore the antioxidant status under high-fat-high-fructose diet-induced oxidative stress in rats (Nasri et al., 2015). Natural administration of *Sardinella aurita* and *Salaria basilisca* protein hydrolysates was shown to disappear oxidative stress for cholesterol-fed rats and alloxan-induced diabetic rats (Ktari et al., 2014). These results suggest that the presence of active peptides in fish protein hydrolysates was effective in increasing the antioxidant status. Free radical scavenging capacity of bioactive peptides in other *in vitro* assays was also observed by several researchers (Fernández-Tomé et al., 2014). Pinto Durango bean (*Phaseolus vulgaris* L.) was found to eradicate reactive oxygen species (ROS) production with alcalase hydrolysates treatment for a 20 h (100 µg/mL) (Fernández-Tomé et al., 2014). Furthermore, the receptor in HepG2 cells for advanced glycation end products (RAGE) showed the lowest expression treated with the complete protein hydrolysates. Treatment with β-casomorphin-7, a milk-derived bioactive peptide, a considerable reduction in H_2O_2 content ($p < 0.05$) and a remarkable increase in the activity of GSH-peroxidase, SOD and catalase of the anti-oxidation system were noticed. Simultaneously, the abatement of free-radical-induced oxidative stress in blood and myocardium and cardiac indexes was also reported (Han et al., 2013). Protective effect of peptides on pancreatic β-cells against intracellular ROS due to a high glucose exposure has also been observed.

3.2 Regulation of glucose uptake and lipid accumulation

Natural peptides were also reported to effectively ameliorate the diabetes symptoms in streptozotocin-induced diabetic rats where blood glucose was markedly decreased after treatment with β-casomorphin-7, a natural peptide (Han et al., 2013). Bioactive peptides were noted to reduce the expression of cytokines such as interleukin-1β and TNF-α in pancreatic β-cells, both of which was generated as the cells were exposed to high glucose in *in vitro* models (Donath et al., 2003). A Chlorella-11 peptide was also able to suppress lipopolysaccharide-induced nitric oxide (NO) and serum TNF-α and inflammation (Cherng et al., 2010). Additionally, it was reported that the common bean peptides can upregulate the expression of insulin-like growth factor 2 (IGF-II), a kind of adipokines in pancreatic β-cells now being believed to play a negative role in the development of obesity-associated insulin resistance and anti-inflammation. The same results were found for protein hydrolysates from muscle fish *Zebra blenny* in alloxan-induced diabetic rats. By the similar assays, significant improvement of insulin sensitivity in T2DM was observed but the glucose-stimulated insulin secretion had not been influenced by chlorella consumption (Jong-Yuh and Mei-Fen, 2005). Peptides from salmon hydrolysate also enhanced glucose uptake in L6 skeletal muscle cells by up to 40% without insulin increase (Roblet et al., 2016).

Table 2. Weight of pancreas, kidney and effect of *Padina tenuis* on total protein, serum insulin level, biochemical parameters, enzymatic parameters in STZ induced albino rats (n = 6). Data are shown as Mean ± SD for triplicate (Arabi et al. 2020).

Index/parameter	NC	DC	RC	PT 25	PT 50
Pancreas Weights ± SD (g)	0.72 ± 0.12	0.25 ± 0.03	0.11 ± 0.00	0.20 ± 0.06	0.23 ± 0.02
Kidney Weights ± SD (g)	1.79 ± 0.11	1.81 ± 0.13	2.22 ± 0.34	1.71 ± 0.22	1.77 ± 0.10
Total Protein (g/dl)	5.95 ± 1.96	10.85 ± 3.49	7.07 ± 0.76	8.20 ± 0.50	6.40 ± 3.51
Serum insulin level (U/mL)	0.07 ± 0.05	0.23 ± 0.04	0.19 ± 0.07	0.16 ± 0.13	0.11 ± 0.08
Total cholesterol (mg/dl)	57.66 ± 7.02	56.00 ± 6.24	52.00 ± 1.73	58.66 ± 3.51	52.50 ± 4.94
TG (mg/dl)	29.33 ± 5.50	44.50 ± 3.53	38.00 ± 5.11	29.00 ± 4.24	30.00 ± 4.24
Serum creatinine (mg/dl)	0.47 ± 0.09	0.75 ± 0.25	1.00 ± 0.16	0.73 ± 0.07	3.69 ± 1.27
Serum urea (mg/dl)	87.66 ± 1.52	63.66 ± 6.11	44.66 ± 4.93	62.66 ± 8.62	70.00 ±18.38
Serum uric acid (mg/dl)	8.76 ± 2.44	5.80 ± 0.34	7.43 ± 1.80	5.26 ± 0.750	7.00 ± 1.73
ALT (u/L)	23.00 ± 1.41	34.50 ± 6.36	37.66 ±18.14	34.33 ± 5.50	94.00 ±11.31
AST (u/L)	3.53 ± 0.63	9.03 ± 0.68	7.20 ± 0.51	2.00 ± 0.62	4.00 ± 0.69
ALP (u/L)	254.50 ±14.84	432.00 ±67.88	580.00 ±18.35	380.00 ± 5.65	25.50 ± 15.76

3.3 Regulation of insulin signaling pathways

Insulin resistance, making cells fail to respond the actions of insulin and reduce or impair insulin-stimulated glucose uptake, needs important therapeutic strategy to be corrected in T2DM. An insulin receptor substrate-1/phosphoinositide-3-kinase/protein kinase B (IRS-1/PI3K/Akt) signaling pathway was found as a main target to correct insulin regulating glucose uptake (Wang et al., 2017). A defect in protein kinase B

(PKB or Akt) signaling that reduces the translocation of GLUT4 to the cellular membrane may be a main impairment of insulin-stimulated glucose uptake under insulin resistance conditions (Govers, 2014). The action mechanism of IRS-1/PI3K/Akt signaling pathways on regulation of blood sugar is illustrated in Figure 2. An *in vivo* assay showed that under insulin resistance of diabetes, phosphorylation level of Akt Ser473 decreases, and insulin signal transduction also significantly abate due to a decrease in insulin receptor concentration (Morino et al., 2008). Therefore, insulin receptor (IR), insulin receptor substrate-1/2 (IRS-1/2), PI3K and Akt all may be efficient targets to regulate downstream signaling cascade to lower blood sugar level. Some evidences reported on the upregulation of GLUT4 in T2DM individuals by natural marine peptides. The effect of aglycin peptide on insulin signaling in the mice skeletal muscle showed that a significant increase in the expression of IR and IRS1 genes, as well as total IR, IRS1, p-Akt protein and membrane GLUT4, was observed. An increase of 75% of basal glucose uptake was found in both normal and insulin-resistant C_2C1_2 cells. B-casomorphin-7 and insulin increased 1.37-fold and 1.62-fold of the expression of GLUT-4 in myocardium, respectively. The peptide GAGVGY, a fibroin derivative, increased both basal and insulin stimulated glucose uptake through enhancement of GLUT1 expression and PI3K-dependent GLUT4 translocation (Kim et al., 2011).

In vivo assays showed that fat accumulation was strongly associated with the inhibition of the PI3k signaling pathway, which was involved in the inhibition of insulin signaling (McCurdy and Klemm, 2013). These results might explain the fact that long-term feeding of marine peptide induced weight loss in obese mice both in healthy and diabetic animal models. In addition, Akt is one of the major downstream targets of PI3K and responsible for the physiological function of insulin in adipocytes (Zhu et al., 2015). Phosphatase and tensin homologue (PTEN) is a lipid phosphatase that downregulates the action of PI3K decreasing insulin signaling, playing a role in regulating glucose metabolism (Butler et al., 2003). A reduction of PTEN was presented with pinto Durango-bromelain bean hydrolysate and its <1 kDa peptide fraction treatments.

3.4 Alpha amylase inhibition

Inhibition of α-amylase enzyme is one of the effective therapeutic approaches in lowering blood glucose level to manage diabetes mellitus. As oral administration of goby fish protein hydrolysates, the α-amylase activity in that of high-fat-high-fructose feed rats is decreased by about sixty two percent. Pinto bean peptides (<3 kDa fraction) and cumin seed-derived peptides also showed α-amylase inhibitory capacity at 62.1% and 24.54%, respectively (Cheung et al. 2015). Some inhibitory peptides and their IC_{50} values as well as sequences have been detected or identified in literature and are illustrated in **Table 3.**

Table 3. The status of marine peptide products in market and clinical trials (Cheung et al., 2015).

Compound	Natural Product/ Derivatives	Source	Applications	Status
Nutripeptin ®/ Hydro MN Peptide®	Natural product	Hydrolysate of fish protein hydrolysate of fish protein	Postprandial blood glucose control	Sold as nutraceuticals
Katsuobushi oligopeptide	Natural product	Pentapeptide from hydrolysate of dried bonito	Antihypertensive	Sold as nutraceuticals
Fish gelatin	Natural product	Hydrolysate of fish collagen and gelatin	Nutrient supplements and bone health	Sold as nutraceuticals

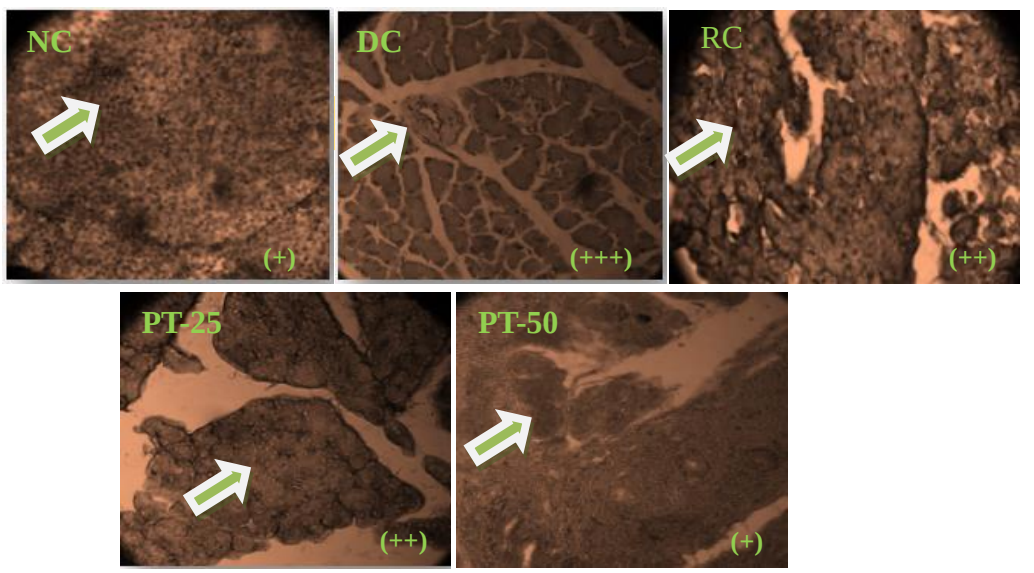

Figure 2. Effect of marine algae *Padina tenuis* (PT) on the tissue architecture of pancreas NC, DC, RC, PT-25 and PT-50 represents Normal control (no treatment), Diabetic Control (Streptozotocin injected), Reference Control (Comet, 200 mg/kg bw), *P. tenuis* 25 mg/kg bw, *P. tenuis* 50 mg/kg bw. The histopathological findings of the

experimental parameters were graded as follows (-) indicates "No abnormality", Extent of injury <5%, (+) indicates "Mild injury", Extent of injury 5-25%, (+ +) indicates "Moderate injury", Extent of injury 25-50%, (+ + +) indicates "Severe injury", Extent of injury >50%. Arrow shows the position of pancreatic islets.

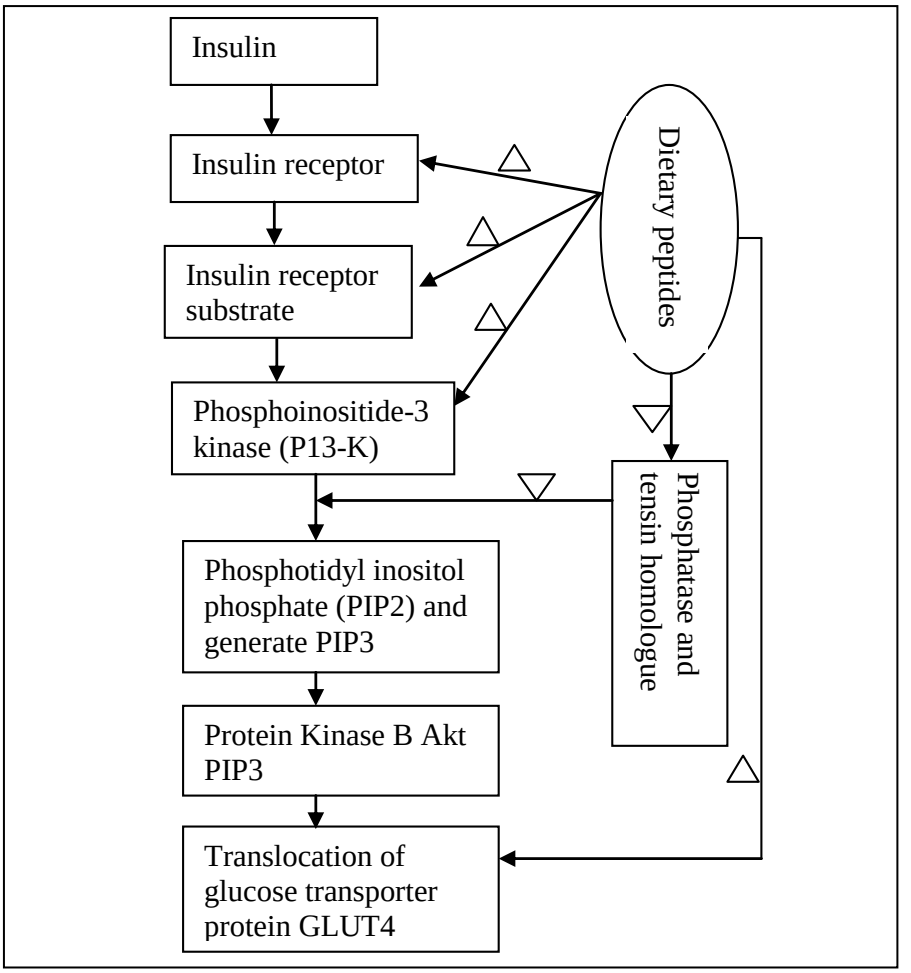

Figure 3. Evidence on the regulation of natural peptides on the insulin-signaling pathways. Note: △ and ▽ mean the natural peptides display upregulation and downregulation on the corresponding bioprocessed, respectively.

In a α-amylase inhibitory study, peptides were identified from proteolytic enzymes hydrolysates of red seaweed laver (*Porphyra* species) using consecutive chromatographic techniques. Two novel peptides were identified as Gly-Gly-Ser-Lys and Glu-Leu-Ser from the seaweed. To validate their α-amylase inhibitory activity,

these peptides were synthesized chemically. The peptides were demonstrated inhibitory activity at IC_{50} value: 2.58 ± 0.08 mM (Gly-Gly-Ser-Lys) and 2.62 ± 0.05 mM (Glu-Leu-Ser). The inhibitory kinetics revealed that these peptides exhibited noncompetitive binding mode. Thus, laver can be a potential source of novel ingredients in food and pharmaceuticals in diabetes mellitus management (Admassu et al., 2018).

4. Marine peptides in diabetes-related complications

Our previous research demonstrated that marine collagen peptides benefit vasodilatation function in patients with T2DM and hypertension (De Luca et al., 2016; Zhu et al., 2013), and that oligopeptides from marine salmon skin reduce fasting blood glucose (FBG) levels. In a study, MCP treatment for 4 weeks significantly lowered the blood glucose level and attenuated endothelial thinning and inflammatory exudation in carotid artery vascular endothelial cells (CAVECs). That study provided the first evidence that the inhibitory effects of MCPs on coupling factors (CF6) and microparticles (MPs), as well as apoptosis-associated factors, may contribute to their protection of cardiovascular endothelial cells in a T2DM rat model. Although T2DM is associated with long-term complications that affect the eyes, kidneys, and peripheral and autonomic nervous systems, CV complications, including hypertension, MI and stroke, are major contributors to mortality in patients with T2DM (Gregg et al. 2014). Intensive control of blood glucose by hypoglycemic agents and/or insulin has been demonstrated to have long-term beneficial effects, reducing the risk of CVD in patients with DM (Inzucchi et al., 2015). The discovery of novel bioactive compounds from marine sources has proceeded at an ever-increasing rate since the first marine compounds were described in the 1980s (Koehnke et al., 2015). Compared to synthetic compounds, these natural products from marine organisms have larger-scale of structural diversity. Bioactive peptides derived from marine organisms are known to exhibit a wide range of physiological or hormone-like biological activities that extend beyond their nutritional value (Vaughan et al., 2015). For example, eicosapentaenoic acid and docosahexaenoic acid, two major omega-3 fatty acids of marine origin, have been demonstrated to effectively lower blood pressure (Mori et al., 2000), treat obesity (Vaughan et al., 2015) and reduce adipose inflammation (White et al., 2015). Furthermore, their use is recommended in guidelines for the management of patients after myocardial infarction. Thus, these observations on MCPs may support novel therapeutic applications for prevention CVD in patients with DM. The most important finding of the present study was that MCPs exert potent protective actions on cardiovascular tissues, such as endothelial cells, in the T2DM rat model. Furthermore, MCPs significantly reduced blood levels of fasting glucose, fasting insulin, total TGs, TC, LDL-C, glycated hemoglobin A1c and free-fatty acids in patients with T2DM (Zhu et al., 2013). Therefore, we concluded that MCP-induced improvement in metabolic dysfunction helped retain regular cardiovascular function in T2DM. These results suggest that the attenuation of impaired endothelial function is due to the prevention of high glucose exposure. Potential molecular mechanisms underlying the protective effect of MCPs were identified in this study. First, it was observed that MCPs depressed the

increases in CF6 levels in blood and CAVECs in diabetic rats. CF6 is a component of mitochondrial ATP synthase that induces vasoconstriction. Intravenous injection of CF6 peptide has been demonstrated to increase blood pressure, potentially by suppressing prostacyclin synthesis, whereas a specific neutralizing antibody against CF6 decreased systemic blood pressure concomitantly with an increase in plasma prostacyclin. Diabetic patients have been identified to have significantly increased plasma CF6 levels, which are correlated positively with blood glucose and lipid levels (Li et al., 2012). CF6 induces insulin resistance, mild glucoseintolerance and elevated blood pressure in mice by binding to the plasma membrane ATP synthase [subunit of ecto-F(1)F(o)complex] (White et al., 2015). In conclusion, to the best of our knowledge, the results of the present study provided the evidence that MCPs protect against cardiovascular endothelial cell injury and alleviate cardiovascular dysfunction in a T2DM rat model by downregulating systemic and local CF6 and MP levels.

5. Future application and prospects

Marine-derived antioxidant peptides and hydrolysates may have great potential to be used as active ingredients in functional foods, food supplements, cosmetic and pharmaceutical industries. They can eliminate the excess free radicals in body and prevent free radical-induced diseases. Some studies reported that the antioxidant effect of protein hydrolysates and peptides isolated from marine Hoki skin gelatin, Tuna back bone and Pacific hake fish fillet are superior to that of α-tocopherol and, in some cases, similar or higher in activity to synthetic antioxidants (BHA and BHT). Synergistic effects of some antioxidant peptides with tocopherols in food and model systems have also been reported (Mendis et al., 2005). Marine-derived hydrolysates and peptides with antioxidant activities can also be used as food additives to reduce oxidative changes during storage in various food products such as frozen foods, fish products and drinks. They also possess unique techno-functional properties such as low viscosity, high solubility and resistance to gel formation. Antioxidants can delay or slow oxidative rancidity in fats, change of food color, vitamins and unsaturated material damage, and they can be directly added to food to improve quality or extend shelf life during the storage and transportation. Researches have shown that marine protein hydrolysates and peptides can be used as natural antioxidants with little or no side effects. One of the promising applications of antioxidant peptides is in seafood processing. They not only effectively control lipid oxidation during storage, but also improve the flavor and increase the nutritional value (Liu et al. 2012). Collectively, the marine antioxidative peptides have potential to expand their health benefits both in functional food and pharmaceutical industry.

6. Concluding remarks

The comprehensive role of marine products particularly marine peptides and relevant functional molecules are evident to contribute significantly for managing diabetes and diabetes related parameters such as cardiovascular diseases, diabetic nephropathy etc. However, the individual compound showing potential therapeutic effects are badly

needed to be assessed further for diabetic management. This review will hint the best use of marine products in diabetic complications.

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Conflict of interests

Authors declare that he does not have any conflict of interest.

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Author's contribution

Md Atiar Rahman has planned, designed, reviewed literature, arranged data and finally prepared the manuscript.

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