Chapter

Advanced Pharmacological Uses of Marine Algae as an Anti-Diabetic Therapy

Thilina Gunathilaka, Lakshika Rangee Keertihirathna and Dinithi Peiris

Abstract

Marine seaweeds are a promising source of bioactive secondary metabolites that can be utilized in drug development and nutraceuticals. Diabetes mellitus is a leading non-communicable disease, and it is the third leading cause of death worldwide. Among the types of diabetes, type 2 became the major health problem as it is associated with severe health complications. Since available oral hypoglycemic drugs cause several adverse effects, it is worth searching for a natural cure with fewer or no side effects that may benefit patients with type 2 diabetes. Among the marine seaweeds, brown and red seaweeds are extensively studied for the anti-diabetic activity compared to the green seaweeds. Bioactive compounds present in marine seaweeds possess anti-diabetic potential through diverse mechanisms, mainly by reducing postprandial hyperglycemia and associated complication. Most of the studies emphasized that the marine seaweeds control the hyperglycemic condition by inhibiting carbohydrate hydrolyzing α-amylase,α glucosidase enzymes, and the inhibitory effect of dipeptide peptidase-4 that are involved in the degradation of incretins. Similarly, bioactive compounds in marine seaweeds can reduce diabetes complications by inhibiting angiotensin-converting enzymes, aldose reductase, protein tyrosine phosphatase 1B enzyme. This chapter focuses on the anti-diabetic potential of marine brown, green, and red seaweeds through different mechanisms.

Keywords: Marine seaweeds, microalgae, bioactive compound, diabetes, drug discovery, mechanisms of action

1. Introduction

The prevalence of diabetes has increased rapidly over the past few years, mainly in low to middle-income countries, and became one of the major causes of premature death worldwide. According to the WHO statistics, 422 million people were estimated as diabetes in 2014, and 1.6 million deaths were reported [1]. The International Diabetes Federation estimated that the world's diabetic population has increased to 592 million by 2035. The largest number of diabetes cases was reported in the Western Pacific region (132 million), while 71.4 million diabetes cases were reported in the South Asian area [2].

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both. It is mainly classified

as insulin-dependent diabetes mellitus (Type 1 DM) and non-insulin-dependent diabetes mellitus (type 2 DM). Type 1 DM is associated with deficiency of insulin, which occurs due to the destruction of pancreatic ß-cells via an autoimmune process. In contrast, type 2 DM is linked with insulin resistance, which reduces insulin utilization by peripheral tissues and results in hyperglycemia and obesity [3]. Type 2 DM became a major health problem worldwide associated with microvascular and macrovascular health complications. Microvascular and microvascular complications include diabetic retinopathy, neuropathy, nephropathy, and cerebrovascular diseases, peripheral arterial diseases, respectively [4]. Therefore, natural therapeutic approaches [5] should be developed to maintain the blood glucose level and long-term complications in patients with type 2 DM.

As currently available treatment regimens for type 2 DM have adverse side effects, it is necessary to search for an effective drug that helps maintain the blood glucose level and complications in patients with type 2 DM. Even though most of the researchers focused on herbal medicine, none have a full beneficial effect on curing patients with type 2 DM [6]. Hence, it is worth emphasizing marine seaweeds as they have been identified as a rich source of promising bioactive compounds synthesized from their biochemical and physiological mechanisms. Besides, most marine seaweeds are survived in extremely harsh environments, which provide enormous potential to produce complex bioactive compounds to withstand extreme conditions. As a result, the composition of the bioactive compounds in marine seaweeds can vary depending on the geographic area and seasonal changes [7]. As most marine seaweeds are a potential source of bioactive compounds with various therapeutic effects, this chapter mainly emphasizes the pharmacological uses of marine algae as an anti-diabetic therapy.

2. Therapeutic targets for type 2 diabetes mellitus

As type 2 DM is a progressive disorder, the search for effective treatments is essential to maintain hyperglycemia and its associated diabetic complication. Insulin resistance and impaired beta-cell function lead to hyperglycemia due to alteration in glucose homeostasis, which in turn cause loss of postprandial glucose control. Therefore, postprandial blood glucose maintenance is essential to manage the hyperglycemic condition and associated complications in type 2 diabetes patients [8]. Postprandial hyperglycemia in type 2 DM patients can be controlled by inhibiting metabolic enzymes such as α-amylase, α-glucosidase, dipeptide peptidase-IV, gut-derived peptide hormones (incretins), and glucagon-like peptide-1 hormone. The glucose-dependent insulinotropic peptide, aldose reductase, angiotensin-converting enzyme, and protein tyrosine phosphatase 1B are involved with diabetic complications [9].

Alpha-amylase and alpha-glucosidase are exo-acting glycoside hydrolase enzymes involved in carbohydrate digestion. Alpha-amylase is involved in the digestion of long-chain carbohydrates, while alpha-glucosidase catalyzes the end step hydrolysis of starch or disaccharides into simple glucose units. Therefore, inhibitors of these enzymes delay glucose absorption, reducing the postprandial blood glucose level [10].

Dipeptide peptidase-IV is a protease enzyme involved in the degradation of incretins, a group of metabolic hormones that stimulate ß cells of Langerhans' islet to release insulin. Incretins are released after nutrient intake, and they delayed gastric emptying and decrease glucagon secretion in addition to stimulation of insulin secretion [11]. Contrarily, the incretin effect on insulin secretion gradually decreases once the patient becomes euglycaemic [12]. Hence, inhibitors of dipeptide peptidase IV are efficient therapeutic means to reduce the degradation of incretins, which help maintain hyperglycemic conditions in type 2 DM.

Similarly, aldose reductase is a rate-limiting enzyme involved in the polyol pathway, which catalyzes glucose reduction into sorbitol in an NADPH-dependent pathway. As the aldose reductase has broad substrate specificity, it binds with glucose and converts it into sorbitol once the hexokinase is saturated and the blood glucose level is high. As a result, produced sorbitol is accumulated within the cells and creates an osmotic effect, leading to cataracts and diabetic neuropathy [13, 14]. Thus, aldose reductase inhibitors prevent secondary diabetes complications.

Similarly, the angiotensin-converting enzyme plays a vital role in the renvital angiotensin-aldosterone system, a hormone system responsible for maintaining the blood pressure and fluid balance in the body. Angiotensin-converting enzymes convert angiotensin I into angiotensin II, a potent vasoconstrictor that mainly acts on arterioles that stimulate the release of aldosterone from the renal cortex and improve sodium reabsorption from the kidney. Therefore, activation of the renin-angiotensin-aldosterone system leads to increased blood pressure, resulting in microvascular and macro-vascular complications in patients with type 2 DM. Thus, inhibitors of the angiotensin-converting enzyme reduce the long-term microvascular and macrovascular complications by lowering the arterial and venous blood pressure [15]. A study reported by Ustundag et al. [16] confirms that angiotensin-converting enzyme activity is increased in diabetic patients compared to normal individuals.

Correspondingly, protein tyrosine phosphatase IB (PTP IB) is a negative regulator of the insulin signaling pathway that dephosphorylate tyrosine residues in insulin receptor and insulin receptor substrate-1. Which in turn reduces insulin sensitivity [17]. Hence, inhibition of the PTP IB enzyme leads to lower blood glucose levels by enhancing insulin sensitivity. The stable hyperglycemic condition in type 2DM patients leads to the accumulation of advanced glycated end products in various tissues resulting in diabetic complications such as neuropathy, nephropathy, retinopathy, and other chronic diseases [18]. Therefore, the natural compounds, which inhibit the formation of advanced glycation end products, would be a promising therapeutic target to suppress the diabetic complications associated with glycated products.

3. Bioactive compounds present in marine seaweeds

Marine seaweeds are categorized into three algal classes; red (*Rhodophyceae*), green (*Chlorophyceae*), and brown algae (*Phaeophyceae*) based on the presence of natural pigments. *Phaeophyceae* contains brown color fucoxanthin pigment, whereas *Rhodophyceae* possess red color pigments phycoerythrin and phycocyanin, and *Chlorophyceae* is rich in green color pigment chlorophyll. Among the three varieties, most marine algae are referred to as "edible" that can be used for human consumption. Asians and South Africans mainly consume these edible seaweeds as a promising complementary and alternative medicine [19].

Recently, marine seaweeds have been identified as a rich source of bioactive secondary metabolites with human health benefits. In particular, polyphenols, sterols, alkaloids, flavonoids, tannins, proteins, peptides, essential fatty acids, enzymes, vitamins, and pigments are extensively synthesized by marine seaweeds. These compounds exhibit significant chemical and biological properties such as anti-diabetic, antioxidant, cytotoxic, anti-fungal, anti-bacterial, anti-coagulant, anti-inflammatory, and antiproliferative activities, etc., [19, 20]. The marine seaweeds are a rich source of sulfated polysaccharides (**Figure 1**), which have been reported to possess beneficial human effects. Fucoidan, alginates, and laminarans

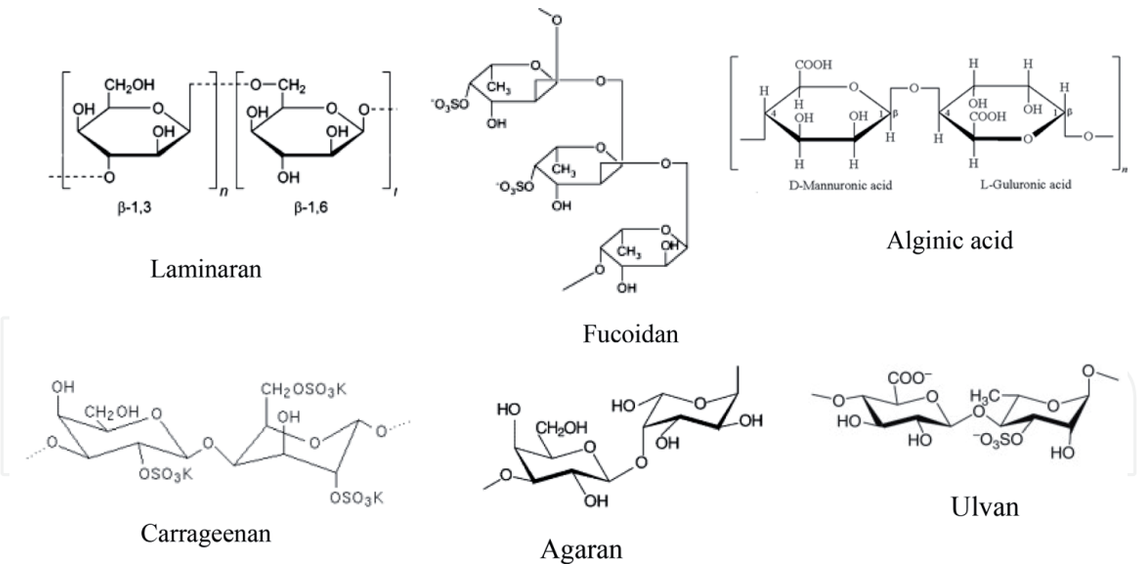

Figure 1.
Chemical structures of sulfated polysaccharides present in marine seaweeds.

are sulfated polysaccharide found in brown seaweeds and reported to exhibit anti-diabetic, antioxidant, and anti-inflammatory activities [21]. Carrageenans and agarans are sulfated polysaccharides found in red seaweeds. Similarly, ulvan is the sulfated polysaccharide found in green seaweeds [22]. The sulfated polysaccharides are known to possess anti-viral, anti-tumor, and anti-coagulant activities [23].

Marine seaweeds are rich in polyphenolic compounds, including flavonoids, bromophenols, phlorotannins, mycosprine-like amino acids, and phenolic terpenoids (**Figure 2**). The mycosprine-like amino acid is a small molecule with hydroxylated aromatic rings. Phlorotannins are polyphenolic metabolites found in brown seaweeds. They can be classified into six subgroups; fuhalols, phlorethols, fucophlorethols, and fucols, eckols, and carmalols based on their linkage between phloroglucinol units and hydroxyl groups. Flavonoids, bromophenol, phenolic terpenoids, phenolic acids, and mycosporine-like compounds are reported to possess antioxidant, anti-diabetic, anti-inflammatory, anti-allergic, and anticancer properties [24–26].

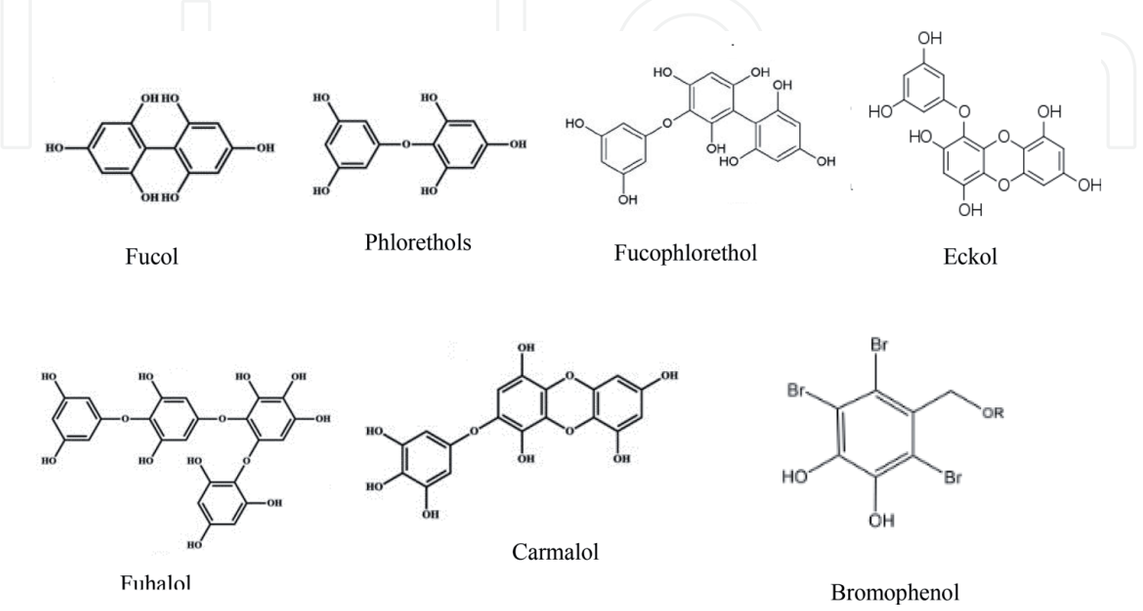

Figure 2.
Organic structures of phlorotannins and bromophenols.

Among the bioactive compounds present in marine seaweeds, marine algae-derived accessory pigments are important as they possess beneficial biological activities [27]. Fucoxanthin is the most abundant accessory pigment found in brown seaweeds and reported to have potent biological activities such as anticancer, antioxidant, anti-diabetic activities due to the presence of unusual allenic bond and a 5, 6-monoepoxide in its structure [21]. Phycobiliproteins, a water-soluble accessory pigment found in red seaweeds, can be divided into three main categories; phycocyanins, allophycocyanins, and phycoerythrin. Phycoerythrins are abundantly found in red seaweeds and reported to possess immuno-modulating and anticancer activities. Similarly, chlorophylls are found in green seaweeds and are said to have antioxidant activity [27].

Similarly, marine algae-derived peptides have been identified to possess a wide range of biological activities such as antioxidant, anti-diabetic, anti-microbial, antihypertensive properties, etc. Hence, most algal-derived proteins have been widely used in food and pharmaceutical industries [28]. The protein content of the marine seaweeds differs depending on the seasonal period and type of species. The brown seaweeds usually contain low protein content compared to the red and green seaweeds. Despite this, some brown algal species such as *Choonospora minima*, *Padina gymnospora*, *Dictyota menstrualis*, and *Sargassum vulgare* possess high protein content up to 10–15%. According to the reported studies, green seaweed contains an average protein content level, ranging between 10–26%. In contrast, the highest protein content was reported in red seaweeds such as *Phorphyra tenure* and *Palmaria palmata*, which was around 47% [29].

4. Anti-diabetic potentials of marine algae

Marine seaweeds have been widely studied for their anti-diabetic potential through different mechanisms due to bioactive secondary metabolites. Several *in-vitro* and *in-vivo* studies have been conducted so far to confirm the hypoglycemic effect of marine algae in addition to its ability to suppress diabetic complications. This section emphasizes the anti-diabetic potential of marine brown, red, and green seaweeds through diverse mechanisms.

4.1 Inhibitory activity of carbohydrate hydrolyzing α-amylase and α-glucosidase enzymes

a. Brown seaweeds

Among the brown seaweeds, "Ecklonia" and "Eisenia" genera have been reported to exert hypoglycemic effects through α-amylase and α-glucosidase inhibitory activities [30]. The observed hypoglycemic activity can be attributed to the presence of phlorotannins; eckol, dieckol, 6,6′-bieckol, phlorofucofuroeckol-A, and phloroglucinol, and 7-phloroeckol [31]. According to the reported studies, methanol extract of *Ecklonia cava* exercises its hypoglycemic effects through the inhibitory activity of α-glucosidase enzymes (IC_{50}–10.7 μM), compared to the standard acarbose used. Similar results were reported with phlorotannins isolated from *Ecklonia stolonifera* against the α-glucosidase enzyme. Dieckol (IC_{50}:1.61 μM) and phlorofucofuroeckol-A (IC_{50}:1.37 μM) isolated from *Ecklonia stolonifera* reported to exhibit the potent inhibitory activity of α-glucosidase enzymes compared to the standard drug (IC_{50}: 51.65 μM). Similarly, eckol (IC_{50}: 11.16 μM) isolated from *Ecklonia maxima* demonstrated strong α-glucosidase inhibitory activity comparable to the isolated phloroglucinol (IC_{50}: 1991 μM). Besides, *Eisenia bicyclis* from genus

Eisenia reported possessing 87% of inhibitory effect on α-amylase at 1 mM concentration in addition to the inhibitory effect on α-glucosidase and advanced glycation end products. Moreover, isolated eckol (IC_{50}: 22.78 μM), dioxinodehydroeckol (IC_{50}: 34.60 μM) and phloroglucinol (IC_{50}: 141.18 μM) from *Eisenia bicyclis* exhibited potent α-glucosidase inhibitory activity [32].

A brown seaweed *Sargassum hystrix* reported to exhibit inhibitory effect on α-amylase IC_{50}: 0:58 ± 0:01 mg/ml; IC_{50} acarbose: 0:53 ± 0:00 mg/ml) and α-glucosidase (IC_{50}: 0:59 ± 0:02 mg/ml; IC_{50} acarbose: 0:61 ± 0:01 mg/ml) enzymes compared to the standard acarbose [33]. This was further confirmed by an *in-vivo* study using streptozotocin-induced rats and observed that the deduction of pre-prandial (186.4 mg/ml) and postprandial (186.9 mg/ml) blood glucose levels at 300 mg/kg concentration comparable to the standard drug glibenclamide (5 mg/kg) (Pre-prandial;195.6 mg/ml; postprandial:104.8 mg/ml) without any adverse effects. Correspondingly, ethanol (150 mg/kg) and aqueous (300 mg/kg) extracts of *Sargassum polycystum* reported to reduce hyperglycaemic condition in diabetic rats [34]. Further studies has reported that a brown seaweed *Ascophyllum nodosum* effectively inhibited α-amylase (IC_{50}: 0.1 μg/ml) and α-glucosidase enzymes ((IC_{50}: 19 μg/ml) due to the presence of phlorotannins [35].

b. Green seaweeds

Green seaweeds belong to the genus "Ulva." They have been reported to possess hypoglycemic activity, and they have been used for various food dishes in Asians due to the presence of high soluble fiber content. The aqueous extract of green seaweeds *Ulva lactuca* (Inhibition-α-amylase: 83.4%; α-glucosidase: 61.81%) and *Ulva reticulate* (Inhibition-α-amylase: 89.1%; α-glucosidase: 76.02%) were effective against α-amylase and α-glucosidase enzymes at a concentration of 100 μg/ml after 8 hours of extraction period at 37 °C in a water bath as it gets more time to release the phytochemicals and colloids to the extract [36]. Similarly, the crude extract of *Ulva ohnoi* exhibited α-amylase inhibition by 41.7% and complete α-glucosidase inhibition at 10 mg/mL [37].

The methanol extract of a green seaweed *Chlorodesmis* inhibited α-amylase enzyme by 72% at 500 μg/ml with IC50 of 408.9 μg/ml without any effect on α-glucosidase enzymes. Similarly, chloroform extract of *Chaetomorpha aerea exhibited a potent inhibitory effect on α-amylase enzyme with* IC_{50} of 147.6 μg/ml. Besides, methanol extract of green seaweeds *Enteromorpha intestinalis (59%) and Cladophora rupestris (14%) exhibited a moderate and lower effect on the α-amylase inhibitory activity at a concentration of* 500 μg/ml [38]. Moreover, crude extracts of green seaweeds *Derbesia tenuissima and Oedogonium intermedium* were reported to exhibit lower α-amylase (53.6% and 49.2%) and potent α-glucosidase (73.98% and 69.5%) inhibitory effect at a concentration of 10 mg/ml [39]. Further studies reported that the green seaweed *Chlorella pyrenoidosa* could suppress the hyperglycaemic condition by inhibiting α-amylase and α-glucosidase enzymes. Besides, a green seaweed *Cladophora rupestris* has been reported to exhibit a hypoglycemic effect through α-amylase and α-glucosidase inhibitory mechanisms [40].

c. Red seaweeds

Among the marine red seaweeds, the genus "Gracillaria" was reported to possess the hypoglycemic effect through the inhibitory effect on α-amylase and α-glucosidase enzymes. Gunathilaka *et al*, [41] reported that the ethyl acetate fraction of red seaweed *Gracillaria edulis* exhibited potent α-amylase (IC_{50}: 279.48 μg/ml) and α-glucosidase (IC_{50}: 87.92 μg/ml) inhibitory activity compared to the

standard acarbose ($IC_{50amylase}$: 87.43 μg/ml; $IC_{50glucosidase}$: 0.38 μg/ml) due to the presence of reported anti-diabetic compound 1H-Indole-2-carboxylic acid,6-(4-ethoxy phenyl)-3-methyl-4-oxo- 4,5,6,7-tetrahydro-isopropyl ester. Further studies reported that the aqueous extract of *Gracillaria edulis* inhibited the α-amylase and α-glucosidase enzyme by 87.86% and 79.55% at a concentration of 100 μg/ml. Similarly, *Gracilaria corticata* and *Acanthophora spicifera* had an inhibitory effect on α-amylase (84.66%; 54.73%) and α-glucosidase (73.53%; 46.86%) enzyme at a concentration of 100 μg/ml [36].

4.2 Inhibitory activity of dipeptidyl peptidase-IV (DPP-IV)

Dipeptidyl peptidase-IV (DPP-IV) is an enzyme involved in the degradation of incretin hormones, maintaining postprandial blood glucose levels. Among three types of seaweeds, brown seaweeds have been extensively reported to possess a dipeptidyl peptidase-IV (DPP-IV) inhibitory effect compared to red and green seaweeds [42].

a. Brown seaweeds

The brown seaweeds *Padina sulcata*, *Sargassum binderi*, and *Turbinaria conoides* have been reported to exhibit a potent inhibitory effect on the DPP-4 enzyme in a dose-dependent manner. The maximum inhibitory effect of *Padina sulcata*, *Sargassum binderi*, and *Turbinaria conoides* were observed as 83.09%, 81.75%, and 76.20%, at a concentration of 10 mg/ml, respectively. Further, crude water extracts of the above three brown seaweeds could secrete glucagon-like peptide-1 (GLP-1) to a greater extent than prevent hyperglycaemic conditions [42]. Similarly, ethyl acetate: methanol fraction (IC50: 0.013 mg/ml) of *Sargassum wightii* has been reported to exhibit an inhibitory effect on DPP-4 enzymes compared to the standard drug diprotein-A (IC50: 0.007 mg/ml) [43]. The methanol extract of *Turbinaria ornate* exhibited a strong inhibitory effect on the DPP-4 enzyme by 55.4% at 80 μg/ml than the standard drug diprotin A (65%) might attribute to the presence of fucoids and sulfated polysaccharides in *T. ornata* [44].

b. Green seaweeds

The previous study conducted by Chin *et al.* [42] reported the inhibitory activity of green seaweed *Halimeda macroloba* on the DPP-4 enzyme. *Halimeda macroloba* inhibited the DPP-4 enzyme by 60.53% at a 10 mg/ml concentration compared to the positive control Berberine (75.92% at 1 mg/mL). Moreover, crude water extract of *H. macroloba* was able to stimulate glucagon-like peptide-1 (GLP-1) secretion.

c. Red seaweeds

The sulfated polygalactans isolated from red seaweeds *Kappaphycus alvarezii* and *Gracilaria opuntia* have been reported to possess the inhibitory effect on the DPP-4 enzyme. According to the results, sulfated galactans isolated from *Gracilaria opuntia* (IC50 0.09 mg/mL) significantly inhibited the DPP-4 enzyme than the sulfated galactans of *Kappaphycus alvarezii* (IC50 0.12 mg/mL) compared to the standard diprotin A (IC50 1.54 mg/mL). The observed activity might be due to the reaction between functional groups of sulfated polygalactan with DPP-4 by H-bonding and hydrophilic interactions [45]. Similarly, aqueous, alkaline, and a mixture of aqueous/alkaline fractions of a red seaweeds *Palmaria palmate* have exhibited a potent

inhibitory effect on DPP-4 enzyme with IC_{50} of 2.52 ± 0.05 mg/ml, 4.60 ± 0.09 mg/ml, and 4.24 ± 0.02 mg/ml respectively [46]. Further studies reported that the red seaweed *Palmaria palmate's protein hydrolysate* had a potential inhibitory effect on the DPP-4 enzyme [40]. These results confirmed the possible inhibitory effect on DPP-4 enzymes of red seaweed extracts.

4.3 Inhibitory activity of aldose reductase (AR)

a. Brown seaweeds

The ethyl acetate fraction of brown seaweed, *Ecklonia stolonifera* has been reported to possess a strong inhibitory effect on aldose reductase enzymes due to the presence of phlorotannins such as 7-phloroeckol and 2-phloroeckol in ethyl acetate fraction [47]. Similarly, phlorofucofuroeckol-A isolated from *Eisenia bicyclis* exhibited a potent inhibitory effect of aldose reductase enzyme (IC50: 6.22 μM). They also confirmed the inhibitory effect of fucosterol in the rat lens. Carotenoids isolated from *Ecklonia stolonifera* exhibited potent inhibitory activity on aldose reductase enzyme (IC50: 18.94 μM) compared to the standard positive control quercetin (IC50: 1.34 μM). The presence of porphyrin derivatives (pheophytin-A and pheophorbide-A) in the dichloromethane fraction of *Saccharina japonica* caused excellent inhibitory effects on aldose reductase (AR) in rat lens [48]. Moreover, fucoxanthin isolated from *Undaria pinnatifida* and *Eisenia bicyclis* reported acting as a competitive inhibitor on the aldose reductase enzyme [49].

b. Green seaweeds

The chloroform and ethanol fractions of green seaweed, *Capsosiphon fulvescens* showed a potent inhibitory action on the AR enzyme [50]. The authors further carried out isolation of compounds, and the isolated compounds (capsofulvesin A, B, and chalinasterol) demonstrated high inhibitory action on AR enzyme with IC_{50} values of 52.53, 101.92, and 345.27 μM, respectively.

c. Red seaweeds

Regarding red seaweeds, the bromophenol compounds present in red seaweeds have been identified as effective therapeutic agents. The bromophenols such as bis (2,3,6-tribromo-4,5 -dihydroxy phenyl) methane, 2,2′,3,6,6′-pentabromo-3′,4,4′,5-tetrahydroxydibenzyl ether, and 2,2′,3,5′,6-pentabromo- 3′,4,4′,5-tetrahydroxydiphenylmethane isolated from red seaweed, *Symphyocladia latiuscula* are well known for their inhibitory effects on aldose reductase. This enzyme is responsible for the fructose formation in the polyol pathway [25].

4.4 Inhibitory activity of protein tyrosine phosphatase 1B (PTP 1B)

a. Brown seaweed

The brown seaweeds belonged to the genus "Sargassum" as reported to exhibit the potent inhibitory activity of PTP 1B enzyme due to the presence of secondary bioactive compounds. Ali *et al*. [51] reported that the hexane fraction (IC_{50}: 1.83 μg/ml) of *Sargassum serratifolium* strongly inhibited the PTP 1B enzyme than the standard ursolic acid (IC_{50}: 1.12 μg/ml). During the compound isolation, three plastoquinones (sargachromenol, sargahydroquinoic acid, and sargaquinoic acid) were identified, and among them, sargahydroquinoic acid exhibited a potent PTP 1B

inhibitory effect (IC50:5.14 μg/ml). Similarly, the chloroform extract of *Sargassum yezoense* (54.4%), *Sargassum fluvellum* (36.1%), *Sargassum horneri* (46.2%), Sargassum *sagmianum (21.4%),* Sargassum *hemiphyllum* (44.1%), and *Sargassum siliquastrum* (14.8%) could inhibit PTP 1B enzymes at 15 μg/ml of concentration [52]. Further, the phlorotannins such as eckol, 7-phloroeckol, and phlorofucofuroeckol-A isolated from *Ecklonia stolonifera, Ecklonia cava*, and *Eisenia bicyclis* could act as non-competitive inhibitors on PTP 1B enzyme [53]. Moon *et al*. [32] further confirmed the inhibitory effect of phlorofucofuroeckol-A (IC_{50}: 0.56 μM), 7-phloroeckol (IC_{50}: 2.09 μM), and eckol (IC_{50}: 2.64 μM) isolated from *Ecklonia stolonifera* and *Eisenia bicyclis. Moreover, fucosterol isolated from Eisenia* bicyclis and *Ecklonia* stolonifera also showed PTP 1B inhibitory effect [54].

b. Green seaweeds

Several studies have been reported to elucidate the anti-diabetic potential of green seaweeds by enhancing insulin sensitivity through the mechanism of PTP 1B inhibition. Among the marine green seaweeds, Crude chloroform and methanol extract of a green seaweed *Derbesia marina* has been reported to exhibit an inhibitory effect on PTP 1B enzyme by 61.7% and 80.65 respectively at a concentration of 15 μg/ml. Further, the crude chloroform and methanol extract of edible green sea lettuce "*Ulva pertusa"* has exhibited potent PTP 1B inhibition at 15 μg/ml by 25.8% and 48.1%, respectively. Similarly, the crude chloroform and methanol extract of *Enteromorpha linza* (42.1%:35.4%) and *Codium adhaerens* (51.5%:71.2%) increased insulin sensitivity by inhibiting PTP 1B enzyme at 15 μg/ml concentration [52]. *Further, the compounds isolated from the green seaweeds belonged to the genus "Caulerpa" had a potent anti-diabetic effect by the mechanism of PTP 1B inhibition.* Racemosin C, Caulerpin, Caulerpic acid isolated from *Caulerpa racemosa,* and Caulersin isolated from *Caulerpa serrulata* have reported significant PTP1B inhibitor [55].

c. Red seaweeds

Most of the red seaweeds belonged to the genus "Chondus" exhibited anti-diabetic activity via PTP 1B enzyme inhibition. According to the recorded studies, chloroform extract of *chondus ocellanthus* and *chondus crispus* inhibited PTP 1B enzymes by 41.5% and 27.6% at a concentration of 15 μg/ml. Similarly, red seaweeds belonged to the genus "Laurencia" had a potential inhibitory effect on PTP 1B enzyme. The methanol extract of *Laurencia okamurae* (33.1%) and chloroform extract of *Laurencia intermedia* (43.3%) could inhibit PTP 1B enzyme at 15 μg/ml of concentration. In addition to that 15 μg/ml concentration of chloroform extract of *Corallina pilulifera*, *Gymnogongrus flabelliformis*, and *Gracillaria textori* inhibited PTP 1B enzyme by 58.3%, 38.6%, and 24.9%, respectively [46]. Further, the compounds bromophenol and 3, 4-dibromo-5-(2-Bromo-3, 4-dihydroxy-6-(ethoxymethyl)benzyl)benzene-1,2-diol isolated from red seaweed, *Rhodomela confervoides* could increase insulin sensitivity via inhibition of PTP 1B enzyme [40].

4.5 Inhibitory activity of angiotensin-converting enzymes (ACE)

a. Brown seaweeds

Phlorotannins eckol, phlorofucofuroeckol-A, and dieckol isolated from brown seaweed, *Ecklonia stolonifera* could inhibit angiotensin-converting enzyme with IC50 values of 70:82 μM, 12:74 μM, and 34:25 μM, respectively. Among the isolated phlorotannins, dieckol acted as a non-competitive inhibitor of ACE [56]. Similarly, the

phloroglucinol isolated from the ethyl acetate fraction of Sargassum (56.96 μg/ml) wightii significantly inhibited the ACE compared to the positive control captopril (51.79 μg/ml) [57]. An amino acid sequence isolated from edible brown seaweed, *Undaria pinnatifida,* could significantly inhibit angiotensin-converting enzymes [57]. The protein-derived hydrolysate of *Undaria pinnatifida* exhibited a potent antihypertensive effect via inhibiting ACE [39]. Further, the enzymatic hydrolysate of *Ecklonia cava* has been reported to show a potent inhibitory effect on ACE with IC50 values from 2.33 up to 3.56 μg/mL [58].

b. Green seaweeds

Among the green seaweeds, few studies have been reported regarding the inhibitory effect on the angiotensin-converting enzyme. Crude and saponified extracts of *Ulva ohnoi*, *Derbesia tenuissima,* and *Oedogonium intermedium* exhibited an inhibitory effect on the angiotensin-converting enzyme. The crude extract of *Ulva ohnoi*, *Derbesia tenuissima,* and *Oedogonium intermedium* had a less potent inhibitory effect at 10 mg/ml. In contrast, the saponified extract of *Ulva ohnoi*, *Derbesia tenuissima,* and *Oedogonium intermedium* inhibited 1.9%, 1.47%, and 7.37% compared to the positive control captopri*l* (6.15% inhibition at 200 μg/ml). However, carotenoids; siphonaxanthin, neoxanthin, 9′*-cis-*neoxanthin, loroxanthin, violaxanthin, lutein, siphonein, α-carotene, and β-carotene present in green seaweeds are found to be poor inhibitors of ACE [37]. Further, a protein-derived hydrolysate of an edible green seaweed *Enteromorpha clathrata* had a potent inhibitory effect on ACE [58].

c. Red seaweeds

The red seaweeds have been widely studied to elucidate the inhibitory effect on angiotthe ensin-converting enzyme, as it plays a crucial role in regulating blood pressure. According to the recorded studies, the aqueous extract at 20 °C of red seaweeds *Lomentaria catenata, Lithophyllum okamurae, Ahnfeltiopsis flabelliformis, and Gracilaria textorii* significantly inhibited the angiotensin-converting enzyme by 98.92%, 89.23%, 73.45%, and 65.40% at a lower concentration of 200 μg/ml. Similarly, the methanol extract at 700C of red seaweeds, *Ahnfeltiopsis flabelliformis, and Laurencia okamurae* has been reported to exhibit a strong inhibitory effect angiotensin-converting enzyme by 97.59% and 78.01% at a concentration of 200 μg/ml. Further, the methanol extract at 70 °C of red seaweeds *Grateloupia filicina, Sinkoraena lancifolia, Grateloupia elliptica, Grateloupia lanceolata,* and *Laurencia okamurae* exhibited an inhibitory effect on ACE by 83.14%, 80.86%,68.13%, 89.04%, and 69.80% at 200 μg/ml of concentration [59]. This study revealed the presence of ACE like inhibitors in red seaweeds. Protein-derived hydrolysate in *Palmaria palmate* (red seaweed) showed marked antihypertensive activity. The antihypertensive activity was exerted via inhibition of angiotensin-converting enzymes [46]. Further, an enzymatic hydrolysate of a red seaweed *Pyropia columbina* exhibited an inhibitory effect on the angiotensin-converting enzyme with an IC50 value of 1.2 mg/ml [58].

4.6 Inhibitory activity of the formation of advanced glycation end products (AGEs)

a. Brown seaweeds

Among the brown seaweeds, *Ecklonia cava* has been extensively studied for its anti-diabetic activity. The phlorotannins isolated from *Ecklonia cava* such as eckol

(IC_{50}: 1.6 × 103 μM), phlorofucofuroeckol-A (IC_{50}: 2.4 × 103 μM), fucofuroeckol A (IC_{50}: 7.4 × 102 μM), and dieckol (IC_{50}: 7.4 × 102 μM) could inhibit the formation of advanced glycation end products comparable to the standard drug aminoguanidine hydrochloride (IC_{50}: 8.1 × 103 μM) [60]. Similarly, the phlorotannins isolated from methanol extract of brown seaweeds *Sargassum polycystum* (IC_{50}: 35.245 μg/ml), Turbinaria Ornate (IC_{50}: 22.7 μg/ml), and Padina pavonica IC_{50}: 15.16 μg/ml) had the ability to suppress the formation of advanced glycation end-products [61]. Further, phlorotannins extracted from the ethyl acetate fraction of *Fucus vesiculosus* (IC_{50}: 0.045 mg/ml) significantly inhibited the AGEs formation compared to the phloroglucinol (IC_{50}: 0.068 mg/ml) [62].

b. Green seaweeds

So far, minimal studies have been reported to demonstrate the inhibitory effect of green seaweeds on the formation of advanced glycation end products. The chloroform, ethanol, and butanol fractions of a green seaweed *Capsosiphon fulvescens* have been reported to exhibit an inhibitory effect on the formation of advanced glycation end-products [50].

c. Red seaweeds

Regarding the red seaweeds, the ethyl acetate fraction (IC_{50}: 586.54 μg/ml) of *Gracillaria edulis* has been reported to exhibit the inhibitory effect on the formation of advanced glycation end products compared to the standard drug rutin (IC_{50}: 11.55 μg/ml) [34]. Similarly, carrageenan extract from red algae could inhibit progressive glycation end product uptake by macrophage-like RAW 264.7 cells [63].

5. Conclusions

Recently, marine seaweeds have been extensively studied for their therapeutic effects due to promising bioactive compounds. Among the non-communicable diseases, diabetes mellitus is the third leading cause of death associated with vascular complications. As it is a progressive disorder, it is necessary to search for an adequate drug for natural resources with minimum side effects. Therefore, this chapter illustrates the different anti-diabetic mechanisms of marine seaweed extracts and their bioactive compounds.

Acknowledgements

The University of Sri Jayewardenepura, Sri Lanka (ASP/01/RE/SCI/2017/50).

Conflict of interest

The authors declare no conflict of interest.

Author details

Thilina Gunathilaka, Lakshika Rangee Keertihirathna and Dinithi Peiris*
Department of Zoology/Genetics and Molecular Biology Unit (Center for Biotechnology), Faculty of Applied Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka

*Address all correspondence to: dinithi@sjp.ac.lk

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