Review

Seaweed-Based Interventions for Diabetic Complications: An Analytical Discourse

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Abstract: Modern sedentary lifestyle has given rise to a number of health issues; diabetes mellitus is one of them, another worldwide emergency, which is usually attributed either by deficiency or by insensitivity of insulin hormone; the master-regulator of blood glucose level. Seaweeds are rich reservoirs of a plethora of bioactive compounds with a great assortment of therapeutic potential. The goal of this communication is to represent the state-of-the-art about what is known for the anti-hyperglycemic properties recognized in seaweeds, emphasizing about their assets of several bioactive principles, their modes of action over targets of pharmacological interest, in addition to their precise extraction procedures. Various bioactive molecules from seaweed origin, mainly polyphenols, can inhibit several drug targets like α-glucosidase, α-amylase, aldose reductase, protein tyrosine phosphatase 1B, angiotensin-converting enzymes and dipeptidyl peptidase-4 to achieve good glycemic control.

Keywords: seaweed, diabetes, bioactive compound, hormone

1. Introduction

Seaweeds, mostly constituted by brown and red macroalgal assemblages, are a great reservoir of a number of natural anti-diabetic agents due to the presence of plentiful amount of polyphenols, vitamins, carotenoids, unsaturated fatty acids, pigments including phycoerythrin, phycobilins and many more with barely any side effects. The propensity of their cell wall to retain excellent quantities of trace elements, as well as other marine minerals makes them legendary as dietary food supplements with immense biomedical interest [1]. In many regions of East Asia, mostly in the coastal countries, seaweeds are taken as a wholesome meal in their delicacy [2]. For example, Japanese used to consume 5.3 g of seaweed per day in their daily diet [3]. Inactive lifestyle, unhealthy dietary choices associated with rapid urbanization has increased the risk of diabetic complications worldwide, verging on epidemic proportions over both the developed and developing nations. Rigorous studies have established seaweeds as skilful defenders against a range of pernicious health issues including hyperlipidemia [4], hyperglycemia [5], breast cancer [6] and other cardiovascular hassles [7].

Tanemura et al. have reported that consumption of the sporophylls of *Undaria pinnatifida* (Wakame) reduces post-prandial blood glucose level, probably by virtue of their plentiful fucoxanthin content [8]. Paradis et al. demonstrated the role of commercial macro algal blend containing *Fucus vesiculosus* and *Ascophyllum nodosum* in insulin sensitivity

and regulation in humans, as measured using Cederholm index after sugar consumption [9]. A study involving Korean population, suggested the relevance of *Undaria pinnatifida* and *Porphyra yezoensis* as anti-diabetic diet [10]. Sanger et al. have elucidated the role of one edible marine seaweed *Halymenia durvilae* in diabetes management [11]. Aqueous extract of *H. durvilae* appeared to show excellent efficiency to inhibit α-glucosidase enzyme, one of the major drug targets for diabetes management, with IC50 value 4.34±0.32 mg/mL. Yan et al. have used the aqueous ethanolic extract of *Enteromorpha prolifera* over streptozotocin-induced type 2 diabetic mice, fed with high-sucrose/high-fat diet [12]. The flavonoid-rich fraction, containing the active principle, EPW3 (<3 kDa), characterized through high-resolution UPLC-Q-TOF-MS/MS system has been reported to diminish the blood glucose level at fasting, enhance oral glucose toleration and reduce liver and kidney injury. They attributed the in behind molecular mechanism through q-PCR analysis and according to the result, EPW3 appeared to boost up the glucose consumption and insulin sensitivity through restraining JNK and by invigorating PI3K/Akt signalling cascades. The diabetes-mitigating properties of six different seaweeds; *Ulva lactuca* (Chlorophyta), *Padina pavonica*, *Sargassum acinarium*, *S. muticum* and *Turbinaria decurrens* (Phaeophyta) and *Pterocladia capillacea* (Rhodophyta) have been checked by Ismail et al. [13]. The maximum anti-hyperglycemic activity has been exerted from the acetone extract of *T. decurrens* with an IC50 value of 4.37 mg/mL (96.1% inhibition potency) in comparison with Acarbose, used as positive control, which inhibits the starch-degrading α-amylase enzyme. Likewise, it has been shown to inhibit the α-glucosidase enzyme at a concentration of 90 mg/mL, with IC50 value of 2.84 mg/mL (97.4% inhibition potency). Hardoko et al. measured the α-glucosidase inhibition potency of the laminaran fraction from *Sargassum duplicatum* with IC50 value of 36.13 ppm, characterization has been done using fourier transform infra-red spectroscopy (FTIR) analysis and λ-max absorption spectroscopy [14]. Mohapatra et al. have emphasized the anti-hyperglycemic effect of ethyl-acetate extract of *Ulva fasciata* through inhibition of α-amylase [15]. Radhika and Priya have emphasized the effect of *Acanthophora spicifera* over alloxan induced diabetes [16]. Recently, another group from Vietnam has studied the role of *Laurencia dendroidea* using 80% methanol for extraction and fractionated with n-hexane, chloroform, ethyl acetate and butanol. The ethyl acetate fraction was with strongest α-glucosidase inhibitory property, probably due to the enormity in polyphenol content in this fraction [17]. The possible mechanism relies on the hindrance of the active sites of the diabetic enzymes by the polyphenolic substances, thereby altering their catalytic efficiency [18].

2. Pathophysiology of diabetes mellitus - The worldwide emergency

Diabetes mellitus (DM), a type of chronic hyperglycemia, is one of the most leading health hazards of this century, characterised by deficiency and resistance of insulin hormone imparting extremity in the blood glucose level. Some other complications associated with DM are hypertension, neuropathy, nephropathy, several vascular disorders and many more [19]. Normally, pancreatic β-cells secrete insulin, which maintains the blood glucose level at its optimum level and promotes body cells to feed glucose for energy production. Loss of insulin sensitivity along with diminution of insulin production leads to blood glucose accumulation at an alarming level, resulting in the outcome of diabetic complications [20]. Based on the etiological point of view, DM is of two types- (i) Type 1 DM, attributed due to auto-immune demolition of the pancreatic β-cells resulting from insulin deprivation, and (ii) Type 2 DM, much more prevalent than the former one [21], accounts for the insulin-insensitivity as well as insulin-resistance of body cells due to excessive glucose production by liver cells, accompanied by poor glucose-consumption by muscle and adipose cells [22]. Current clinical approach mainly focuses on the manipulation of several starch-hydrolysing enzymes (for example, pancreatic α-amylase) as well as glucose-consumers like intestinal α-glucosidase to combat this multifactorial disorder [23].

3. Bioactive principles from seaweeds with anti-diabetic potency

Seaweeds are mostly marine macroalgae, majorly categorised into three distinct groups based on their pigment composition- green algae (Chlorophyta), red algae (Rhodophyta) and brown algae (Phaeophyta) [24]. They are a great asset of a number of active principles like polyphenols, poly- and monounsaturated fatty acids, carotenoids, dietary

fibres among others with immense health benefits, having anti-hyperglycemic, antioxidant, cytotoxic as well as anti-inflammatory properties [25]. Some of which are discussed in the following section.

3.1 *Monounsaturated fatty acids (MUFA)*

Although the exact mechanism for MUFA-mediated diabetes management is not clear cut, it has been attributed to up-regulate several glucose transporter proteins (for example GLUT1, GLUT4) thereby promoting intracellular glucose uptake besides restricting destruction of pancreatic-β cells [26]. Sabin et al. have reported enhanced insulin sensitivity due to MUFA-mediated interference over IRS/PI3K insulin pathway in association with elevated GLUT4 translocation across the cell membrane [27]. Dietary MUFAs also play a significant role in diabetes prevention through the amelioration of glucagon-like peptide (GLP-1) [28] and adiponectin levels [29].

3.2 *Polyunsaturated fatty acids (PUFA)*

As about 2% of the dry weight of seaweed constitutes different kinds of PUFAs, most of which are omega-3 (Figure 1) and omega-6 fatty acids, important components for healthy human diet [30]. But the members of Chlorophyta (except: *Ulva* sp.) have lesser lipid content in comparison with other phaeophycean and rhodophycean members [31]. The possible mechanism relies upon the improvement of insulin sensitivity and rate of glucose consumption [32]. Omega-3 PUFA can also check insulin insensitivity by inhibiting toll-like receptors (TLR) like TLR-2 and TLR-4 [33]. Other long chain PUFAs alleviates the concentration of tumour necrosis factor-α and pro-inflammatory interleukin-1ra, whereby elevating the concentration of different anti-inflammatory cytokines like interleukin-10 [34]. Moreover, Jump et al. discussed the genetic interplay behind the PUFA-mediated hyperglycemic mitigation [35]. They have highlighted the role of a number of transcription factors like sterol-regulatory element-binding protein-1c, hepatic nuclear factors and liver X receptor etc. which are integral part of fat and sugar metabolism.
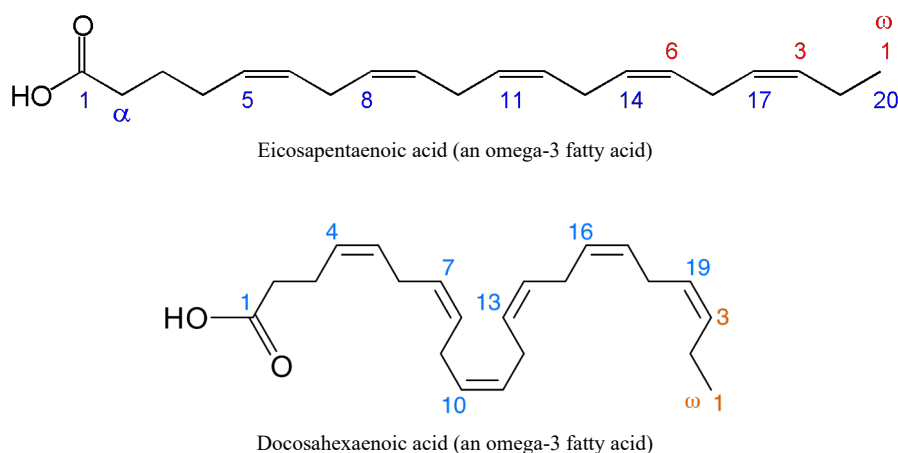

Eicosapentaenoic acid (an omega-3 fatty acid)

Docosahexaenoic acid (an omega-3 fatty acid)

Figure 1. Different seaweed-derived PUFAs of biomedical interest

3.3 *Dietary fibres*

Including dietary fibres in daily diet not only reduces body weight, glycemic level and inflammation, but also enhance satiety as well as hormonal interactions [36]. Several seaweed-based food items like arroz-caldo (porridge) incorporated with lambda-carrageenan (Figure 2) [37], Nori (*Porphyra*) has been proved to have anti-hyperglycemic potential [38]. Vaugelade et al. have studied the effects of dietary-fibre extracts from *Palmaria palmata*, *Laminaria digitata* and *Eucheuma cottonii*, over insulin sensitivity and intestinal glucose absorption in pigs [39].
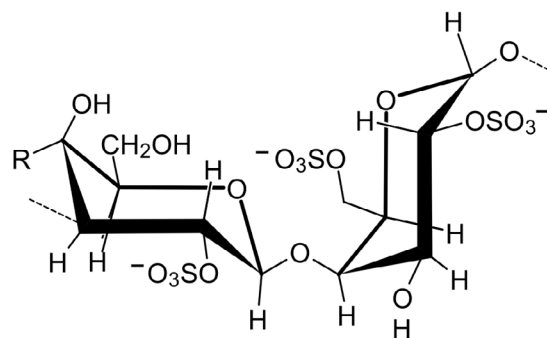
Figure 2. Structure of lambda carrageenan

3.4 *Polyphenols*

Polyphenols from seaweeds are mainly constituted by phlorotannins, derived from phloroglucinol subunits. The phenol groups, present in their molecular architecture, are responsible for mitigation of diabetes related oxidative stress. Some important seaweed-derived polyphenols, with immense therapeutic interest are eckols, fucophlorethols, fucols and carmalols (Figure 3) [25].
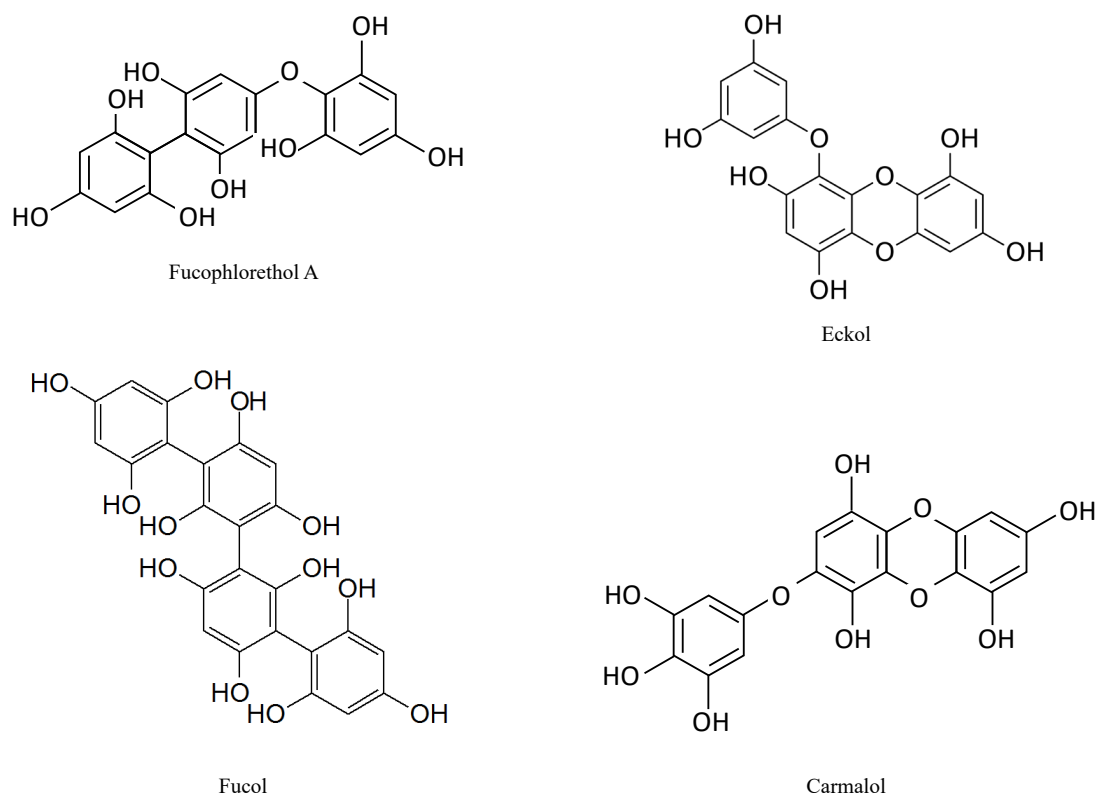

Fucophlorethol A

Eckol

Fucol

Carmalol

Figure 3. Different phlorotannins of seaweed-origin

3.5 *Carotenoids*

Brown seaweeds involve a great array of pigments and the authoritative one is fucoxanthin (Figure 4). It has tremendous anticarcinogenic, antihyperglycemic, antioxidative potential due to the presence of oxygenic functional group and novel allenic bond in their structural organization.
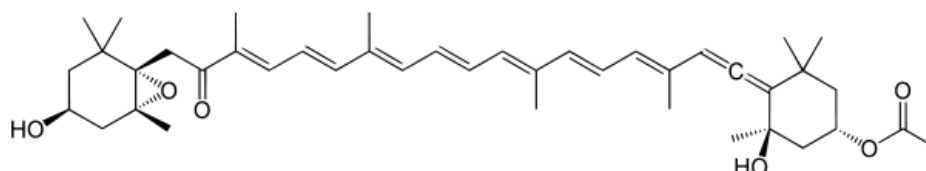

Figure 4. Molecular structure of fucoxanthin

4. Novel trends for bioactive compounds extraction from seaweeds

Recent technological approaches mainly lean on four different techniques for extraction of therapeutically relevant compounds from seaweeds, which are- Supercritical Fluid Extraction (SFE), Ultrasound-Assisted Extraction (UAE), Subcritical Water Extraction (SWE) and Microwave-Assisted Extraction (MAE) [25].

4.1 *Ultrasound-assisted extraction (UAE)*

UAE can be done under low temperatures, desired for extraction of thermolabile active principles and the working time is comparatively less [40], which makes it affordable than the other sophisticated trends [41]. This technique deals with the application of ultrasonic damage of biological matrix, triggering the release of active principles. The frequency usually ranges between 20 kHz to 100 kHz. Application of this substantial frequency leads to cavitation and implosive burst of cells. In this approach, the goal is mainly achieved by two ways- either by using ultrasonic probe (direct sonication) operating at a frequency of 20 kHz or by using ultrasonic bath at frequency of 40-50 kHz (indirect sonication). The difference is that during the indirect method, the sample is plunged with ultrasonic bath, whereas the direct method deals with the direct injection of the ultrasonic probe within the sample [42]. This technique is efficiently utilised for antioxidants and pigment extraction under the regime of proper solvents with appropriate solid to solvent ratio.

Dang et al. standardised the protocol for ultrasonic release of antioxidants from the alga *Hormosira banksii* [43]. The highest yield has been obtained at a temperature of 30°C for one hour under 150W power. Similarly, the highest yield has been obtained from the red seaweed *Laurencia obtusa* after treatment at 50°C temperature for 45 minutes with 250 W power and with a solvent to seaweed ratio of 30:1 mL/g [44]. However, Mittal et al. have shown that amalgamation of maceration with ultrasonication results in enhanced phycobiliproteins extraction from another red seaweed *Gelidium pusillum*, probably due to better cell lysis [45].

4.2 *Microwave-assisted extraction (MAE)*

In this trend, the energy of microwave gets absorbed by the polar molecules present over the cell surface, triggering cellular disruption, mainly due to dipole rotation and ionic conduction. Disrupted cells fasten the mass transfer reciprocated with solvent diffusion [46]. MAE extraction procedure can be operated either in open or in closed system. The former one is safer and economically viable as it relies on the application of atmospheric pressure and here large sample sizes can be processed at less time and is also worthy for thermolabile components [47]. This technique is mainly employed for polyphenol and polysaccharide extraction under optimized parameters like degree of biomass processing, solid-to-solvent ratio, temperature and frequency of microwave etc. [48].

4.3 Subcritical water extraction (SWE)

This method deals with a very short exposure (5-10 minutes) of samples under temperature (50-200°C) and pressure extremes (50-300 psi) for extraction, so the mobile phase (liquid) is maintained at its critical range, below its boiling point [41]. Here, water is used for extraction, instead of other costly organic solvents, therefore is usually attributed for extraction of non-polar compounds. del Pilar Sanchez-Camargo et al. have reported that enzymatic pre-treatment of samples can enhance the yield of several polyphenols of therapeutic interests [49]. But, this is not preferable for the extraction of thermolabile compounds as it is operated under high temperatures. Plaza et al. prepared a comparative data set with six different macroalgae [50]. They pointed out the fractions obtained at higher temperatures impart better antioxidant property probably due to Maillard and Caramelization reactions.

4.4 Supercritical fluid extraction (SFE)

Here, the reactions are operated above the critical range in terms of temperature, pressure and other characteristics of both liquids and gases [41]. Supercritical CO_2 (SC-CO_2) is used as a solvent and better yield is achieved through increased mass transfer due to low viscosity and higher diffusion coefficient of supercritical CO_2. The extra-added advantage is the less critical temperature and pressure of CO_2, which prevents the degradation of extracted principles [51]. This technique is usually employed for the extraction of fatty acids, tocopherols, phytosterols, carotenoids, triglycerides and phenolic compounds [49].

The advantages and limitations of these extraction methodologies are summarized in Table 1.

Table 1. The advantages and limitations of extraction techniques

Extraction techniques	Advantages	Limitations	References
Ultrasound-Assisted Extraction (UAE)	• Suitable for extraction of thermolabile compounds as it is operated under low temperature. • Solvent requirement and working time are lesser. • The surface area of contact between the solvent and extractable compound increases for better penetration of solvents into the sample matrix to release bioactive compounds.	• Acoustic cavitation may promote free radical synthesis, which in turn triggers lipid oxidation. • Large scale extraction is quite difficult. • Huge power demand.	[52]
Microwave-Assisted Extraction (MAE)	• Shorter extraction time and a higher extraction yield of the target analytes. • Simultaneous analyze of several samples at a time. • Close- or open-vessel system can be used for extraction.	• Methanol, ethanol and ethyl acetate absorb the microwave energy and convert it into heat, which helps to break cell wall for easy penetration of analytes into the solvent matrix. • Operating costs are high with high impurities obtained in the extract. • Ready-to-use extract.	[53]
Subcritical Water Extraction (SWE)	• Water can be used for extraction instead of organic solvents in an environment-friendly way. • Permeability of solvent into the material is enhanced results in higher extraction yield.	• Extraction temperature facilitates the yield of polyphenols and antioxidant activity. • High temperature promotes the degradation of thermolabile compounds.	[25]
Supercritical Fluid Extraction (SFE)	• As CO_2 is cheap and easily available at high purity, it also lacks toxicity and flammability. • The rapid penetration through the pores of heterogeneous matrices due to higher diffusion coefficient and lower viscosity. • For the preservation of bioactive compounds and preventing degradation, CO_2 has low critical temperature and pressure.	As supercritical CO_2 (SC-CO_2) only extracts compounds of low polarity and non-polar compounds, it is better to use the combination of SC-CO_2 and a low amount of co-polar solvents like ethanol and methanol for getting better results.	[25]

5. Pharmacological targets to achieve good glycemic control

Some important drug targets for controlling post-prandial hyperglycemia are in the following section.

5.1 *Sugar-hydrolysing enzymes*

The synergistic activity of a number of glycoside hydrolases like α-amylase, α-glucosidase helps in digestion of starch within human body. Enzyme α-amylase hydrolyses the α-bonds of the dietary starch granules, whereas α-glucosidase catalyses the final step for glucose synthesis from dietary starch and other disaccharides. Thus, restriction of these enzyme activities alleviates the post-prandial blood sugar level and can be employed as an efficient anti-hyperglycemic drug target [54].

Lee and Jeon emphasized the potential of family Lessoniaceae and the genus *Ecklonia* sp. as these groups are a great natural reservoir of a wide variety of polyphenols including phlorofucofuroeckol-A, 6,6′-bieckol, 7- phloroeckol, etc. [55]. They tested the massive inhibitory property of methanolic extracts of *Ecklonia cava* and *E. stolonifera* over α-glucosidase activity, using acarbose as positive control. They have shown that crude extracts of seaweed-derived phlorotannins including dieckol, diphlorethohydroxycarmalol effectively reduce the post-prandial blood sugar level in diabetes-induced mice. Consistently, Abdelsalam et al. advocated the better anti-hyperglycemic efficacy of dieckol (IC50 value of 1.61 μM) and phlorofucofuroeckol-A (IC50 value of 1.37 μM) in comparison to standard drug acarbose (IC50 value of 51.65 μM) [56]. They have also demonstrated the anti-diabetic property of eckol (IC50: 11.16 μM) extracted from *Ecklonia maxima*. They have performed a comparative analysis with the metabolites of *Eisenia bicyclis* (Arame), and reported fucofuroeckol A (IC50 value of 42.91 μM) to be better α-amylase inhibitor than dioxinodehydroeckol (IC50 value of 472.70 μM). Moon et al. elucidated α-amylase inhibitory property of polyphenols like dieckol, eckol, and 7-phloroeckol from *Eisenia bicyclis* [57]. Gotama et al. studied that phlorotannins from *Sargassum hystrix* effectively reduces preprandial (186.4 mg/mL) and post-prandial (186.9 mg/mL) blood glucose levels of streptozotocin-induced diabetic mice at a dose of 300 mg/kg without any significant effect over body-weight, compared to the standard drug glibenclamide, which at a dose of 5 mg/kg keeps the pre-prandial blood glucose level at 195.6 mg/mL and postprandial glucose level at 104.8 mg/mL [58]. Consistent with that, Senthilkumar et al. have shown that aqueous extract of *Padina boergesenii* alleviates the action of gluconeogenic enzymes better than glibenclamide in hyperglycemic rats [59]. Recently, Gunathilaka et al. have suggested the α-amylase and α-glucosidase inhibitory role of the polyphenol-rich extracts of *Chnoospora minima* [60].

5.2 *Aldose reductase*

The enzyme aldose reductase catalyses sorbitol synthesis from glucose using NADPH cofactor via polyol pathway. Intracellular sorbitol extreme may serve as a potential biomarker for Type 2 DM and causes diabetic neuropathy. On that account, inhibitors of aldose reductase are of immense therapeutic interest [61].

Jung et al. examined the rat lens aldose reductase inhibitory activity of the dichloromethane fraction of *Saccharina japonica*, which has been achieved probably due to the presence of porphyrin compounds like pheophytin-A and pheophorbide-A [62]. The carboxyl group (not linked with phytyl group) at the C-172 position of the porphyrin ring is responsible for this inhibitory property of pheophorbide-A. Lee et al. worked with the ethyl acetate fraction of *Eisenia bicyclis* over human recombinant aldose reductase and the result revealed better inhibition potency in comparison with reference drug epalrestat [63].

5.3 *Dipeptidyl peptidase-4*

This enzyme helps in lowering the incretin levels, like glucagon-like peptide-1 (GLP-1), a gut hormone which stimulates insulin release to control hyperglycemic blood sugar level among the patients suffering Type 2 DM. Interestingly, the culmination of GLP-1 over insulin secretion successively deteriorates when blood glucose level reaches up to euglycemic level. Hence, inhibition of dipeptidyl peptidase-4 may significantly enhance GLP-1 level, promoting insulin secretion sustaining glucose homeostasis [64].

Maneesh et al. advocated the DPP-4 inhibitory activity of ethyl acetate: methanol fraction of *Sargassum wightii*

due to richness in phenolic content [65]. Unnikrishnan et al. evaluated the DPP-4 enzyme inhibitory property of the methanolic extract of *Turbinaria ornata* with 55.4% efficiency at a concentration of 80 μg/mL in comparison with reference drug diprotin A (65%) [66].

5.4 *Protein tyrosine phosphatase 1B (PTP 1B)*

PTP 1B is a negative regulator of the insulin signalling cascade, present on the cytosolic face of the membrane of endoplasmic reticulum [56]. The insulin receptor is a classic example of receptor tyrosine kinase family proteins, which when binds to insulin, autophosphorylates itself in its specific tyrosine residues triggering several downstream signalling reactions. But PTP 1B, through dephosphorylation renders the insulin receptor inactive. Therefore, inhibition of PTP 1B may remove this hindrance over insulin signalling pathway [67].

Ali et al. evaluated the PTP 1B inhibitory activity of the hexane fraction (IC50 value of 1.83 μg/mL) of *Sargassum serratifolium* [68] in comparison with positive control ursolic acid (IC50 value of 1.12 μg/mL). Later, from the hexane fraction, they isolated three different quinones; sargachromenol, sargahydroquinoic acid and sargaquinoic acid. Of these three, sargahydroquinoic acid possesses the highest PTP1B inhibitory activity (IC50 value of 5.14 μg/mL) in the treatment of Type 2 DM. Feng et al. worked with another brown seaweed *Dictyopteris undulata*, and isolated 12 different stigmastane-type steroids; of which, (24S)-7b-methoxy-stigmasta-5,28-diene-3b,24-diol and (24S)-7a-methoxy-stigmasta-5,28-diene-3b,24-diol exhibit anti-hyperglycemic activity [69].

5.5 *Angiotensin-converting enzyme*

This enzyme catalyses the synthesis of angiotensin II into angiotensin I and is an integral part of the renin-angiotensin-aldosterone system. The former one stimulates aldosterone release from adrenal cortex, intensifying water and sodium absorption which is consistent with elevating blood pressure level, leading to several microvascular and macrovascular problems, common among Type 2 DM patients. So, inhibition of this enzyme may help to keep the blood pressure under control among hyperglycemic sufferers [70].

Thomas and Kim worked with *Ecklonia stolonifera* [71]. The results revealed the phlorotannin-rich fraction containing eckol (70.82 ± 0.25 μM), dieckol (34.25 ± 3.56 μM), and phlorofucofuroeckol-A (12.74 ± 0.15 μM) exerts inhibitory activity over angiotensin-converting enzyme. Among which, dieckol inhibits noncompetitively. Therefore, it can be a potential candidate to mitigate diabetes-associated blood pressure deviation. Paiva et al. have reported the better efficiency of the protein hydrolysate fraction (IC50 value of 0.5 mg/mL) of *Fucus spiralis* to inhibit angiotensin-converting enzyme, in comparison with reference drug captopril (IC50 value of 0.163 mg/mL) [72]. Similarly, phloroglucinol (IC50 value of 56.96 μg/mL) containing ethyl acetate fraction of *Sargassum wightii* has greater efficacy to inhibit angiotensin-converting enzyme, in comparison with the positive control captopril (IC50 value of 51.79 μg/mL) [73].

5.6 *Suppression of advanced glycation*

Advanced glycation is a complex process, the end product of which leads to several vascular disorders associated with diabetic complications in addition to renal failure and other chronic symptoms. Thus, inhibition of the formation and cumulation of advanced glycation end products may diminish the diabetic problems to some extent [74].

Shakambari et al. have evaluated the phlorotannin-mediated inhibition of advanced glycation end product formation in glucose-induced diabetic *Caenorhabditis elegans* [75]. They conducted their study with three different taxa, and the results revealed *Padina pavonica* (IC50 value of 15.16 ± 0.26 μg/mL) has better inhibitory property than the other two strains; *Turbinaria ornata* (IC50 value of 22.7 ± 0.3 μg/mL) and *Sargassum polycystum* (IC50 value of 35.245 ± 2.3 μg/mL) in comparison with positive control thiamine (IC50 value of 263 μg/mL). Sugiura et al. have studied the antiglycation activities of phlorotannins-rich extracts of *Ecklonia cava*, which have inhibitory action over fluorescence stained advanced glycation end products formation [76]. In addition, some recent works with seaweeds for the prospect of anti-diabetic drug development, are stipulated in Table 2.

Table 2. Recent works with seaweeds for the prospect of anti-diabetic drug development

Seaweed	Active principles	Mode of action	Extraction solvents	References.
Enteromorpha prolifera	Flavonoids	Reduces blood glucose level by upregulating IRS1/PI3K/AKT pathway and suppressing JNK1/2 pathway in liver	95% ethanol	[12]
Turbinaria decurrens	Cyclotrisiloxane, hexamethyl	Antioxidant activity. α-amylase (96.1%) and α-glucosidase (97.4%) inhibitory property.	Acetone	[13]
Sargassum duplicatum Turbinaria decurens	Laminaran, fucoidan	α-glucosidase inhibitory property.	85% ethanol (ethanol and seaweed at a ratio of 1 : 4)	[14]
Ulva fasciata	-	In vitro α-amylase inhibitory property.	Ethyl acetate	[15]
Laurencia dendroidea	-	α-glucosidase inhibitory property. DPPH radical scavenging properties comparable with a commercial antidiabetic drug (gliclazide).	80% aqueous methanol	[17]
Undaria pinnatifida	Fucoxanthin	Alleviation of visceral fat mass, hepatic glucose production and hyperinsulinemia. Amelioration of hepatic glucose storage and fatty acid oxidation.	Ethanol	[77]
Ulva rigida	Polyphenols	Alleviation of post-prandial blood sugar level. Antioxidant activity.	Ethanol	[78]
Polyopes lancifolia	Bis (2,3 dibromo-4,5 dihydroxybenzy-l) ether	Reduces blood-glucose uptake. α-glucosidase inhibitory property.	Methanol-water (8 : 2, v/v, 1 L)	[79]
Ishige okamurae	Diphlorethohydroxycarmalol	α-glucosidase and α-amylase inhibition.	80% methanol	[80]
Sargassum horneri	Fucoidan	Maintains the blood-glucose level in an insulin dose-dependent manner.	70% ethanol	[81]
Alaria esculenta	-	DPP-4 inhibitory property $(91.3 \pm 0.1\%)$	Ethanol	[82]
Ulva rigida	-	Upregulates GLP-1 secretion and GLP-1 synthesis	Ethanol	[82]
Codium fragile	-	α-glucosidase inhibitory property. Promotes phosphorylation of AMP-activated protein kinase (AMPK). Ameliorates glucose utilization in myotubes.	Water	[83]
Undaria pinnatifida	Sulfated polysaccharides	Stimulates the glucose absorption in insulin-insensitive HepG2 cells. Reduces fasting blood glucose levels, relieve insulin resistance, Upregulates hepatic glycogen synthesis in HFD/STZ-induced hyperglycemic mice.	95% ethanol	[84]
Cystoseira compressa	Phlorotannins	Reduces serum glucose, liver malondialdehyde level and inhibit α-amylase, glucosidase enzymes alongside.	-	[85]
Ecklonia cava	Dieckol	Activation of Akt and AMPK signalling pathways.	80% aqueous ethanol	[86]
Ecklonia maxima	Fucoidan	Mixed type inhibitor of α-glucosidase.	Distilled water	[87]
Bryothamnion seaforthii	Lectin	Exerts hypoglycemic and hypolipidemic effects. Reduces insulin insensitivity, Stimulates the action of pancreatic β-cell toward oxidative stress.	-	[88]

6. Epilogue

In this article, we have tried to account for the mountainous health benefits of seaweeds, emphasizing their ability for diabetes management. In addition, the precise pathophysiology of diabetes mellitus and the targets of therapeutic interest have been taken into consideration. Different bioactive compounds from seaweeds with anti-hyperglycemic effect and novel technologies for their extraction procedure have also been discussed. These green extraction techniques have the potential for their industrial implementation. But protocol optimization is the major task for different samples to get better yield with desired chemical composition in an affordable way. These bioactive principles from macroalgal origin and their mechanism of action are quite similar to other known anti-hyperglycemic drugs. Their propensity to hamper the working scheme of several carbohydrate-hydrolytic enzymes like α-amylase and α-glucosidase provides quality control to the rate of sugar digestion in quite a similar fashion to reference drug acarbose; while the amelioration of insulin perception and incretin hormones stimulation are related to metformin and other DPP-4 inhibitors respectively. Moreover, bioactive compounds from seaweed may also exert their potentiality by enhancing cellular glucose consumption, impeding the activity of enzymes like aldose reductase, DPP-4 and PTP1B, retarding AGE formation, β-cell cytoprotection, anti-obesity action and the associated inflammatory problems as well. Hence, seaweeds and seaweed-derived bioactive principles possess stupendous prospective to be used in Type 2 DM management either as a part of dietary intake or as purified therapeutic supplements.

Acknowledgment

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