







# Hypoglycaemic Molecules for the Management of Diabetes Mellitus from Marine Sources

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**Abstract:** Diabetes mellitus (DM) is a chronic metabolic disorder recognized as a major health problem globally. A defective insulin activity contributes to the prevalence and expansion of DM. Treatment of DM is often hampered by limited options of conventional therapies and adverse effects associated with existing procedures. This has led to a spike in the exploration for potential therapeutic agents from various natural resources for clinical applications. The marine environment is a huge store of unexplored diversity of chemicals produced by a multitude of organisms. To date, marine microorganisms, microalgae, macroalgae, corals, sponges, and fishes have been evaluated for their anti-diabetic properties. The structural diversity of bioactive metabolites discovered has shown promising hypoglycaemic potential through in vitro and in vivo screenings via various mechanisms of action, such as PTP1B,  $\alpha$ -glucosidase,  $\alpha$ -amylase,  $\beta$ -glucosidase, and aldose reductase inhibition as well as PPAR alpha/gamma dual agonists activities. On the other hand, hypoglycaemic effect is also shown to be exerted through the balance of antioxidants and free radicals. This review highlights marine-derived chemicals with hypoglycaemic effects and their respective mechanisms of action in the management of DM in humans.

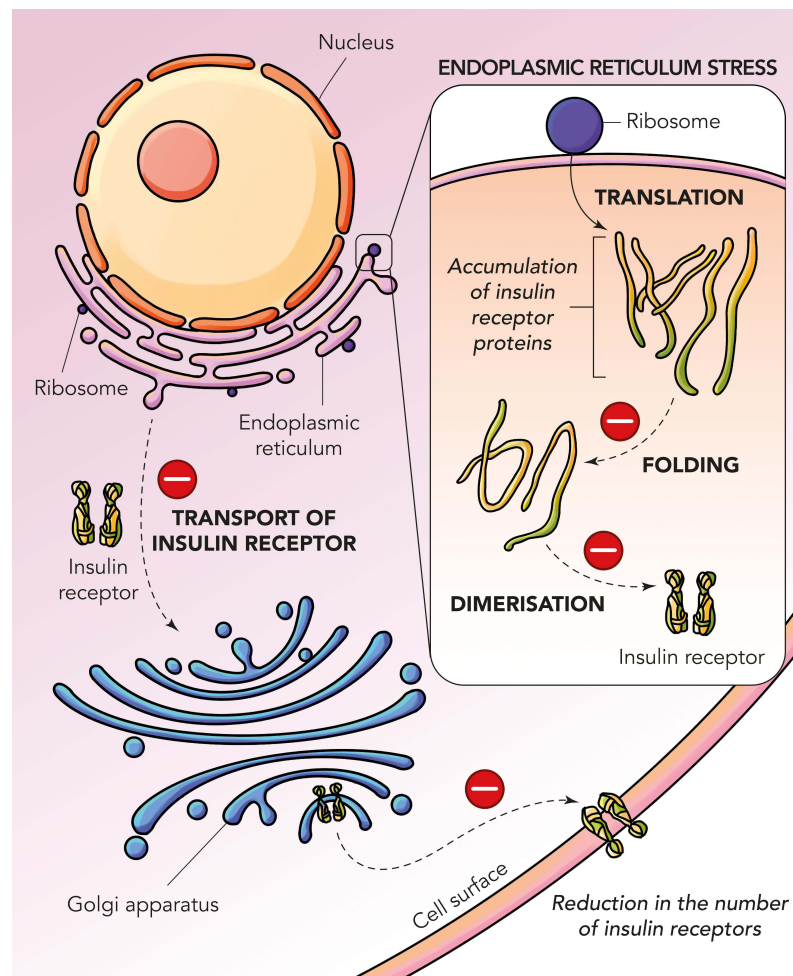
**Keywords:** diabetes mellitus, marine organisms, bioactive metabolites,  $\alpha$ -amylase inhibition,  $\alpha$ -glucosidase inhibition, PTP1B inhibition, antioxidants

## Introduction

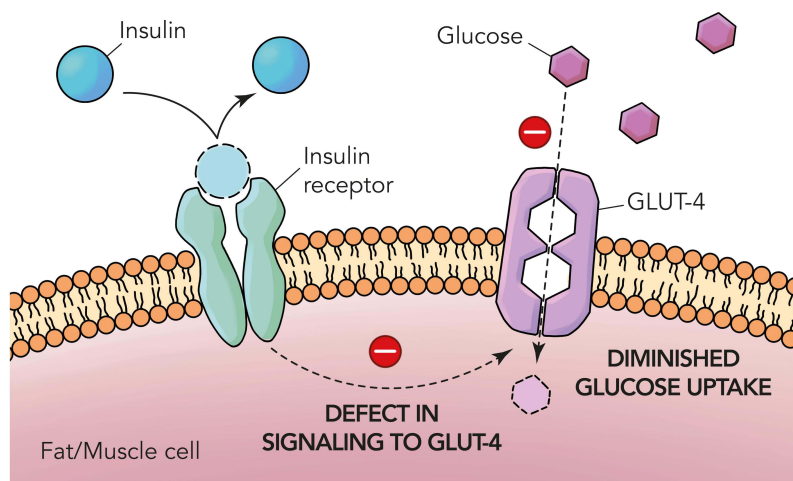
Diabetes mellitus (DM) is one of the chronic metabolic disorders, which often has been recognized as a major health problem globally due to unrelenting hyperglycaemia which contributes to morbidity and mortality.<sup>1,2</sup> The International Diabetes Federation reported that approximately 425 million adults suffered from diabetes in 2017, and by 2045 it is expected to hit 629 million.<sup>3</sup> According to the World Health Organization (WHO), the number of diabetics rose from 108 million in the year 1980 to 422 million in the year 2014. Prevalence of diabetes has been on the rise more rapidly in low- and middle-income countries as compared to high-income countries. Diabetes has been the principal cause of blindness, kidney disease, heart diseases, stroke, and lower limb amputations. There has been a 3% agewise increase in the diabetes-related mortality rates between the years 2000 and 2019. The severity of this disease is associated with microvascular complications causing destruction of neurons, retina, and nephrons affecting nerves, eyes, and kidneys.

This metabolic disorder is also associated with heart-related problems caused by multiple genetical factors and environmental factors,<sup>4-6</sup> such as oversecretion of fats, proteins, and carbohydrate in an individual.<sup>7</sup> DM is a disease of the endocrine system caused by the decreased secretion of insulin by the  $\beta$ -cells.<sup>8</sup> Insulin is produced and secreted by  $\beta$ -pancreatic cells<sup>2</sup> which function by stimulating glucose uptake and synthesis of lipid.<sup>9-11</sup> Persistently elevated blood glucose levels in diabetes can result from either defective insulin role or defective insulin secretion, or both.<sup>6</sup> DM is classified into type-1 (T1DM) and type-2 (T2DM) where T1DM occurs due to the damage of  $\beta$ -cells caused by an autoimmune response with no insulin production.<sup>12</sup> The triggering factors for such a response remain unknown, and it could result from both genetic and environmental factors.<sup>13</sup> Patients with T1DM are fully dependent on insulin therapy for life. In T2DM, the  $\beta$ -cells are either not capable of generating insulin sufficiently for proper functioning of the cells or the body has undergone resistance towards insulin usage. Insulin resistance has been a key factor in the pathogenesis of T2DM (Figure 1). In this case, adopting a healthy lifestyle by regular exercising and a low-calorie diet, together with daily insulin injections and prescribed drugs, may help patients to control the progression of the disease. This type of DM is associated with obesity occurring due to a sedentary lifestyle and high-calorie diet. T2DM has a higher prevalence compared to T1DM, accounting for greater than 90% of all diabetes cases.<sup>8</sup> Pharmacological strategies investigated for controlling T1DM include inhibition of gluconeogenesis, increasing glucose transportation, stimulating the release of insulin, and bringing about reduction in the glucose absorption specifically in the intestines.<sup>14</sup>

Glycaemic regulation is crucial as it is important to keep the blood glucose levels at an optimum. Defects in the signalling mechanisms of GLUT4 leads to diminished levels of glucose intake by the muscle and fat cells (Figure 2) increasing the burden



**Figure 1** Mechanisms leading to insulin resistance in diabetes mellitus.



**Figure 2** Pathophysiology of type 2 diabetes mellitus.

on the beta cells to produce more insulin. This progressive cascade of events over a period results in the pathogenesis of diabetes. Regulation of glucose levels in diabetics can be improved using insulin supplements and other anti-hyperglycaemic medications, either separately or combined.<sup>15</sup> The pharmaceutical industry utilizes modern technology to develop new drugs through high-throughput synthesis and combinatorial chemistry-based drug development. Since the 1980s, pharmaceutical companies, despite a considerable effort towards research and development of newer drugs, are still facing challenges to increase drug productivity and efficiency.<sup>16</sup> Some of the existing drugs have been found to be either less effective or known to cause lethal side effects.<sup>17</sup>

Therefore, there has been a considerable amount of interest in the development of anti-diabetic drugs from natural products, with keen focus on exploring the marine environment for more substitutes. Marine bioresources are rich sources of bioactive constituents such as polyunsaturated fatty acids, polyphenols, proteins, sulphated polysaccharides, sterols, and pigments due to the extreme conditions and active interactions in the marine environment.<sup>18–22</sup> Several studies have reported on the potential of marine drugs as a possible therapeutic option for the management of diabetes and related conditions. The importance of marine-derived metabolites has been the topic of discussion by several authors as they lay the basis for the discovery of potent, novel agents for the treatment of diabetes. For instance, in addition to exhibiting anti-viral and anti-microbial properties, macroalgae are known for synthesizing antioxidants which are used to control low blood pressure, hypolipidemia.<sup>23,24</sup> These marine plants have been also reported to synthesize terpenoids, alkaloids, and peptides, associated to various *in vivo* pharmacological activities.<sup>25</sup> Marine sponge is a source for cytarabine which is known to exhibit anti-cancer activity used in the treatment of lymphoma and acute myelocytic leukemia,<sup>26,27</sup> ziconotide that is useful for treating pain sensations, whether acute or chronic,<sup>28</sup> and vidarabine which is used for the treatment of herpes.<sup>29</sup> This shows the potential of marine natural resources. Therefore, this review highlights the various compounds that possess hypoglycaemic effects to manage DM in human.

## Methodology

Data collection for the published studies on the bioactive components of marine organisms was carried out in PubMed-indexed and Google Search databases using the topic search term (marine\* OR bioactive\* OR algae\* OR sponges\* OR fungal\*) AND organisms AND (hypoglycemic\* OR antidiabetic\* OR antioxidant\* OR antiinflammatory\*) on 30th September 2020. Each paper's title, year of publication, abstract, authors, and digital object identifier (DOI) were thoroughly screened to filter out duplication, and only publications related to this manuscript were eventually considered.

## Anti-Diabetic Mechanisms of Marine Biomolecules in Modifying Enzyme Function in Carbohydrate Metabolism

$\alpha$ -Glucosidase, aldose reductase,  $\alpha$ -amylase, dipeptidyl peptidase 4, glucose-6-phosphatase, glycogen synthase kinase-3 $\beta$ , glucose transporter 4 (Glut4), hexokinase, and *N*-acetyl-glycosaminidase are the enzymes which are notably involved in

the metabolism of glucose. These enzymes play a vital role in inhibiting the diabetic effects in both animal model assays and patients.<sup>30–37</sup>  $\alpha$ -Amylase and  $\alpha$ -glucosidase are majorly utilized for the breakdown and digestion of carbohydrates. The reduction or delay of post-prandial hyperglycaemia is triggered by reducing glucose absorption and inhibiting the carbohydrate breakdown or hydrolases particularly in the gastrointestinal tract.

Alpha-glucosidase inhibitors act along the brush border membrane in the small intestines through competitive inhibition. Therefore, these agents are typically called competitive inhibitors. Generally, they are saccharides that break down sugars. The inhibition is typically observed on enzymes that are essential to digest sugars. A common example of these enzymes would be the alpha-glucosidase enzymes. The mechanism by which the alpha-glucosidase enzyme works is by breaking down sugars to monosaccharides.<sup>30</sup> Aldose reductase,<sup>38</sup> the initial enzyme involved in the polyol pathway, converts glucose to fructose. When the concentration of glucose increases in the cells, aldose reductase converts glucose into sorbitol which is oxidized to fructose by sorbitol dehydrogenase. The mechanism by which aldose reductase functions is typical of a cytosolic NADPH-dependent oxidoreductase which assists in the reduction of sugars. The enzyme generally reduces monosaccharides to sorbitol.<sup>31</sup> Enzymes such as dipeptidyl peptidase 4, glucose-6-phosphatase, hexokinase, maltase, and sucrase, which are involved in the glucose metabolism, can be used to investigate the anti-diabetic effects of biomolecules. DPP-4 inhibitors act by reducing the levels of the hormone glucagon and in turn blood glucose levels. Additionally, the principal action of DPP-4 inhibitors is to raise the level of the hormone incretins, namely GLP-1 and GIP. These actions will result in the inhibition of the hormone glucagon. These cascades eventually result in the increased release of insulin.<sup>32</sup> In addition, Glut4 plays a role in the transport of glucose regulated by insulin, while glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) mediates the addition of phosphate molecules onto threonine and serine amino acid residues and has been associated with diseases such as T2DM, Alzheimer's disease, cancer, and inflammation.<sup>39</sup> In anti-diabetic assays tyrosine phosphatase-1B (PTP1B) is a common protein target. The protein is a non-transmembrane enzyme utilized as a therapeutic target for diabetes, obesity, and breast cancer, and the enzyme plays a significant role both as a negative insulin regulator and in leptin signalling. Aldose reductase and protein tyrosine phosphatase also function as long-term energy storage.<sup>40,41</sup> The PTP1B enzyme reduces the activation state of the insulin receptor kinase by unlocking the insulin signalling leading to the post-receptor signalling inhibition in tissues responding to insulin, leading to the development of T2DM.<sup>2,42–44</sup> Clinical values such as plasma glucose level, plasma insulin, total cholesterol, concentrations of triacylglycerol, blood pressure, body weight, and histopathology of intestine are usually assessed in diabetic animal models and/or patients.<sup>7,45–50</sup> Screenings of these parameters mainly target possible compounds for treating T2DM, whereas identification of molecules with pancreatic  $\beta$ -cell-protective effect through reduction of oxidative processes and inflammation could help in screening for the more severe T2DM.<sup>2</sup>

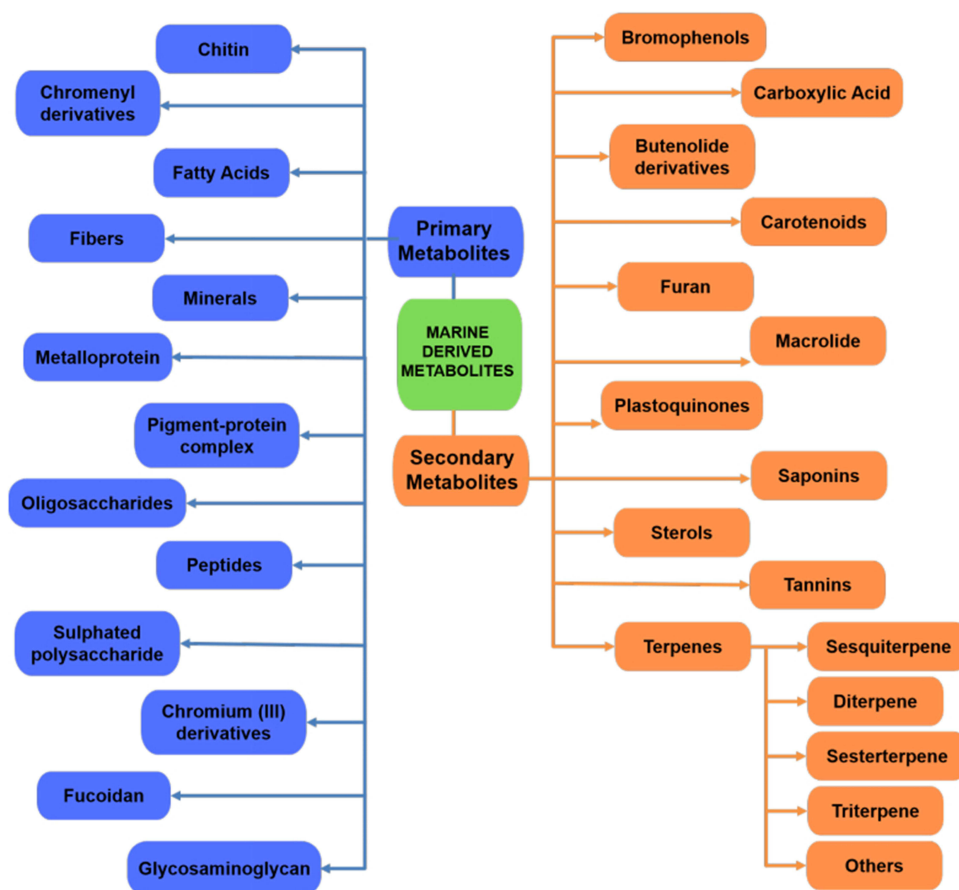
## Primary and Secondary Marine Metabolites Having Anti-Diabetic Activity

Several bioactive metabolites of marine origin have been investigated over the years. This section provides an overview of various categories of bioactive compounds that have been investigated for their anti-diabetic activity using various enzyme-guided anti-diabetic assays. The overall structure of this section is shown in the schematic diagram in [Figure 3](#).

### Primary Metabolites

#### Chitin

A study by Nguyen et al investigated six kinds of chitinous materials which were used as sole carbon/nitrogen (C/N) sources for producing  $\alpha$ -glucosidase inhibitors (aGI) by *Paenibacillus* sp. TKU042.<sup>51</sup> Demineralized crab shell powder (deCSP) and shrimp shell powder (deSSP) as the C/N source produced the highest aGI productivity in the culture supernatants. Compared to acarbose (1095  $\mu\text{g mL}^{-1}$ , 74%), fermented deCSP (38  $\mu\text{g mL}^{-1}$ , 98%) has a higher maximum inhibitory activity and a lower  $\text{IC}_{50}$  against the  $\alpha$ -glucosidase in the intestine of rat. However, there was no inhibitory activity against porcine  $\alpha$ -amylase and *Bacillus subtilis*  $\alpha$ -amylase. Hence, fermented deCSP is a good candidate for anti-diabetic drugs. On the other hand, unfermented deCSP was tested for the presence of  $\alpha$ -glucosidase inhibition, and there was no activity observed, which may have been due to aGI produced by the fermentation process.<sup>51</sup> Homogentisic acid (HGA) isolated from squid pens fermented by four species of *Paenibacillus* is a type of non-sugar-based  $\alpha$ -glucosidase inhibitor,<sup>52</sup> and has a higher  $\alpha$ -glucosidase activity compared to acarbose.<sup>53</sup> [Table 1](#) exhibits the properties of chitin from *Paenibacillus* sp. TKU042.



**Figure 3** Schematic flowchart summarizing the various marine-derived metabolites.

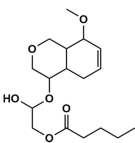
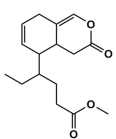
## Chromenyl Derivatives

Two chromenyl derivatives, 11-(3,4,4 $\alpha$ ,5,8,8 $\alpha$ -hexahydro-8-methoxy-4-methyl-1H-isochromen-4-yloxy)-11-hydroxyethylpentanoate (CD-1) and methyl 9-(4,4 $\alpha$ ,5,8-tetrahydro-3-oxo-3H-isochromen-5-yl)hexanoate (CD-2) were isolated from the spineless marine cuttlefish, *Sepiella inermis*.<sup>54</sup> The anti-hyperglycaemic efficacies of chromenyl chemotypes were evaluated using the carbolytic enzymes inhibition such as  $\alpha$ -glucosidase and  $\alpha$ -amylase as well as dipeptidyl peptidase IV (DPP-IV). Inhibition of the carbolytic enzymes reduced the absorption of carbohydrates in the intestine followed by DPP-IV inhibition, which is crucial for the secretion of insulin. CD-1 showed greater DPP-IV,  $\alpha$ -glucosidase, and  $\alpha$ -amylase inhibitory potential compared to CD-2.<sup>54</sup> The study concluded that CD-1 could be beneficial in managing hyperglycaemic-related disorders by maintaining the glucose homeostasis. Characteristics of CD-1 and CD-2 are shown in [Table 2](#).

**Table 1** Microbial-Derived Chitin Possessing Anti-Diabetic Potential

| Species                         | Compound/Extract | Structure | Mechanism of Action              | Reference |
|---------------------------------|------------------|-----------|----------------------------------|-----------|
| <i>Paenibacillus</i> sp. TKU042 | deCSP            |           | $\alpha$ -glucosidase inhibition | [51]      |

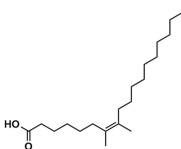
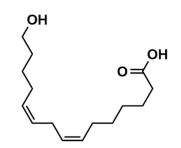
**Table 2** Invertebrate-Derived Chromenyl Derivatives Having Anti-Diabetic Potential

| Species   | Compound/Extract  | Structure   | Mechanism of Action  | Reference |
|---|---|---|--|-----------|
| <i>Sepiella inermis</i><br>(spineless cuttlefish) | 11-(3,4,4 $\alpha$ ,5,8,8 $\alpha$ -hexahydro-8-methoxy-4-methyl-1H-<br>isochromen-4-yloxy)-11-hydroxyethylpentanoate |  | $\alpha$ -glucosidase inhibition<br>$\alpha$ -amylase inhibition<br>dipeptidyl peptidase-IV (DPP-IV)<br>inhibition | [54]      |
|   | methyl9-(4,4 $\alpha$ ,5,8-tetrahydro-3-oxo-3H-isochromen<br>-5-yl)hexanoate  |  |  |           |

## Fatty Acids

Two fatty acids, 1,3-dipalmitolein and *cis*-9-octadecenoic acid, isolated from internal organ of sea cucumber, *Stichopus japonicus*, demonstrated potent  $\alpha$ -glucosidase inhibition activity.<sup>55</sup> 1,3-Dipalmitolein has a more potent inhibitory activity against *Saccharomyces cerevisiae*  $\alpha$ -glucosidase than *cis*-9-octadecenoic acid. The inhibitory activity is affected by the number and position of double bonds in fatty acids. An even number of unsaturated fatty acid has a weaker inhibitory activity compared to an odd number.<sup>54</sup> Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) isolated from marine microalgae *Isochrysis galbana* and *Nannochloropsis oculata* controlled lipid and glucose metabolism in diabetic rats.<sup>2</sup> Omega-3 fatty acid, eicosapentaenoic acid present in various microalgae (eg *Chlorella zofingiensis*, *Chlorella protothecoides*, and *Nitzschia laevis*) can be used as a possible preventive agent in patients with diabetic retinopathy as well as other ocular diseases.<sup>56</sup> High amounts of DHA and EPA may contribute to the reduction in weight, blood glucose, triacylglycerol, and cholesterol levels in diabetic rat models.<sup>49</sup> Unsaturated fatty acids such as 7(Z)-octadecenoic acid and 7(Z),10(Z)-octadecadienoic acid have potent  $\alpha$ -glucosidase activity and mildly inhibited intestinal sucrase and maltase.<sup>57</sup> Two unsaturated fatty acids isolated again from *Sillago japonicus*, 7(Z)-octadecenoic acid and 7(Z),10(Z)-octadecadienoic acid, were found to possess a mild rat-intestinal sucrase and maltase inhibitory activity.<sup>57</sup> These compounds are highlighted with their mechanisms of actions in Table 3. The fatty acids also inhibited *Saccharomyces cerevisiae*  $\alpha$ -glucosidase with IC<sub>50</sub> values of 0.51 and 0.67  $\mu\text{g mL}^{-1}$ , respectively, and *Bacillus stearothermophilus*  $\alpha$ -glucosidase with IC<sub>50</sub> values of 0.49 and 0.60  $\mu\text{g mL}^{-1}$ , thus showing potential as therapeutic agent in treating DM.<sup>57</sup>

**Table 3** Invertebrate-Derived Ether Derivatives Having Anti-Diabetic Potential

| Species                                   | Compound/Extract                    | Structure   | Mechanism of Action   | Reference |
|---|-------------------------------------|---|---|-----------|
| <i>Stichopus japonicus</i> (sea cucumber) | 7(Z)-octadecenoic acid              |  | $\alpha$ -glucosidase inhibition<br>intestinal sucrase inhibition<br>maltase inhibition | [54]      |
|   | 7(Z),10(Z)-<br>octadecadienoic acid |  |   |           |

Furthermore, synthetic oxo-fatty acids such as (7E)-9-oxohexadec-7-enoic acid and (10E)-9-oxohexadec-10-enoic acid can be used in the management of diabetes by inducing anti-diabetic gene programmes in the adipocytes.<sup>58</sup>

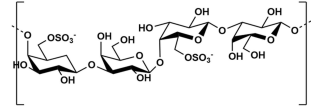
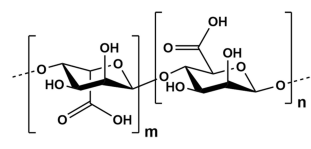
## Fibres

High consumption of dietary fibre can reduce the incidence of type 2 diabetes mellitus (T2DM).<sup>59,60</sup> The recommended amounts of fibre for healthy individuals and diabetic patients are 30 g day<sup>-1</sup> and 50 g day<sup>-1</sup>, respectively.<sup>61,62</sup> In the management of T2DM patients, small amounts of seaweed consumption can achieve high fibre intake with a low glycaemic load.<sup>63</sup> A serving of 8 g of seaweed can meet 12.5% of a person's daily fibre intake.<sup>63</sup> Diabetics who consumed seaweed supplements containing *Undaria pinnatifida* and *Saccharina japonica* were found to have reduced blood glucose levels, blood lipid levels and increased antioxidant enzyme activities.<sup>64</sup> Similarly, consumption of a large amount of dietary fibre reduced insulin resistance biomarkers.<sup>65</sup> Dietary fibre is crucial in managing metabolic disease like diabetes as its post-prandial glycaemic responses in human subjects that consume arroz-caldo with lambda-carrageenan were reduced compared to control groups.<sup>66</sup> Nori (genus *Porphyra*) reduced sharp blood glucose peak and glycaemic response from 100% to 68% in healthy volunteers who consumed carbohydrate (white bread).<sup>67</sup> Dietary porphyran isolated from the red alga *Porphyra yezoensis* enhanced glucose metabolism in diabetic patients by increasing the level of adiponectin.<sup>68</sup> Algal polysaccharides (three seaweed fibres of different viscosities) isolated from *Palmaria palmata*, *Euclima cottonii*, or *Laminaria digitata*, were compared to purified cellulose. Among the polysaccharides, only high viscous alginates decreased the blood glucose level and insulin responses in pigs.<sup>69</sup> Isolated alginates from *L. digitata* lead to decreased glucose absorption of up to 50% over 8 h by the reduction of blood glucose and insulin responses. Sodium alginate formulation has a potential to manage T2DM as it can reduce the average daily consumption of macronutrients and saturated fat in individuals such as healthy, over-weight, and obese people.<sup>70</sup> Consumption of alginate-based supplements can reduce blood glucose levels.<sup>71,72</sup> Table 4 shows samples of marine-derived fibres.

## Minerals

Many macroalgae species such as *Kappaphycus alvarezii* and *Euclima denticulatum* contain magnesium (Table 5). Every 100 g of dried macroalgae can provide around 30% to 90% of magnesium.<sup>73</sup> The magnesium present in the red

**Table 4** Macroalgae-Derived Fibres with Anti-Diabetic Potential

| Species                   | Compound/Extract | Structure   | Mechanism of Action | Reference |
|---------------------------|------------------|---|---------------------|-----------|
| <i>Porphyra yezoensis</i> | Porphyran        |  | na                  | [68]      |
| <i>Laminaria digitata</i> | Alginates        |  | na                  | [69]      |

**Abbreviation:** na, not available.

**Table 5** Macroalgae-Derived Magnesium Possessing Anti-Diabetic Potential

| Species   | Compound/Extract | Structure | Mechanism of Action | Reference |
|---|------------------|-----------|---------------------|-----------|
| <i>Kappaphycus alvarezii</i><br><i>Euclima denticulatum</i> | Magnesium        | Mg        | na                  | [73–75]   |

**Abbreviation:** na, not available.

macroalgae possesses hypoglycaemic activity. Barbagallo et al proposed that the higher the concentration of free magnesium in the intracellular region, the lower the fasting blood glucose level.<sup>74</sup> In addition, Barbagallo et al also proposed that magnesium is involved in the glucose metabolism as well as in insulin homeostasis.<sup>74</sup> Ramadass et al also found that serum magnesium level is inversely proportional to HbA1c levels, a parameter to diagnose type 2 diabetes.<sup>75</sup>

## Metalloprotein

Vanadium-containing proteins (VCPs) isolated from the sea cucumber, *Apostichopus japonicus*, are known to manage insulin resistance and decrease fasting blood glucose and serum insulin levels.<sup>76</sup> High-fat high-sugar diet (HFSD) mice treated with VCP were documented to have reduction in body weight. In addition, the diabetic rats fed with VCP diet had lower adipose tissue weight. VCP administration also reduced fasting blood glucose and increased insulin sensitivity in HFSD mice. It also increased serum adiponectin levels and reduced TNF- $\alpha$ , resistin, and leptin levels.<sup>76</sup> The study evidenced that VCP exhibited anti-diabetic activity by the downregulation of hyperglycaemia and adipokines. Some examples of metalloproteins are shown in Table 6.

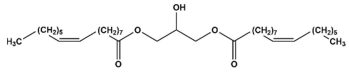
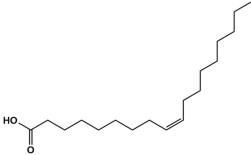
## Pigment-Protein Complex

Phycocyanin isolated from *Spirulina fusiformis*, a microalga, is known to reduce the elevated blood glucose level.<sup>77</sup> Gershwin and Belay report that phycocyanin is one of the biopigments having anti-hyperglycaemic effect.<sup>78</sup> Table 7 shows the phycocyanin from *Spirulina fusiformis*.

## Oligosaccharides

Oligosaccharides isolated from a brown seaweed, *Sargassum confusum*, administered for 30 days and 60 days in HFSD-fed hamsters, decreased fasting blood glucose.<sup>79</sup> It exhibited anti-diabetic effect through the regulation of insulin receptor substrate 1/phosphatidylinositol 3-kinase and c-Jun N-terminal kinase pathways. *Sargassum confusum* was found to

**Table 6** Marine-Derived Metalloproteins Having Anti-Diabetic Potential

| Species                     | Compound/Extract        | Structure  | Mechanism of Action              | Reference |
|-----------------------------|-------------------------|--|----------------------------------|-----------|
| Sea cucumber internal organ | 1,3-dipalmitolein       |  | $\alpha$ -glucosidase inhibition | [76]      |
|                             | cis-9-octadecenoic acid |   |                                  |           |

**Table 7** Microalgae *Spirulina fusiformis*-Derived Pigments and Their Anti-Diabetic Potential

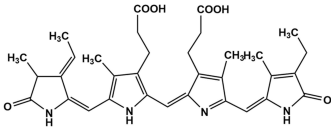
| Species                     | Compound/Extract | Structure   | Mechanism of Action | Reference |
|-----------------------------|------------------|---|---------------------|-----------|
| <i>Spirulina fusiformis</i> | Phycocyanin      |  | na                  | [73–75]   |



exhibit anti-diabetic activity in HepG2 cells in vitro and in vivo using hamsters.<sup>79</sup> The administration of *S. confusum* reduced body weight compared to normal control group. The oral glucose tolerance test showed that *S. confusum* treatment also improved the impaired glucose tolerance of the HFSD-fed hamsters. Furthermore, *S. confusum* also has some effect on the mRNA expression in signalling pathways by reducing the expression of the gene (JNK1 and JNK2) in the treatment group compared to the model group in the hepatic cells. Hence, *S. confusum* can help to enhance the hepatic insulin resistance as well as the hypoglycaemic effect by controlling the pathways of IRS1/P13K and JNK. *Sargassum confusum* exhibited high anti-diabetic activity due to its low molecular weight.<sup>79</sup> Kumar et al proposed that there is a relationship between the blood glucose-lowering action and the low total cholesterol level after the treatment of *S. confusum* for 60 days.<sup>80</sup> Moreover, Oh et al reported that *S. confusum* reduced inflammation and, thereby, maintained normal insulin secretion in a long-term HFSD-induced animal model.<sup>81</sup> Table 8 summarizes the marine-derived oligosaccharide anti-diabetic mechanism of action.

## Peptides

Peptides play a major role in diabetics. Oligopeptides isolated from salmon skin (*Oncorhynchus kern*) were investigated for their anti-diabetic effects in a rat model.<sup>2</sup> The administration of oligopeptides reduced fasting blood glucose levels and apoptosis of pancreatic islet cells where the serum levels of TNF- $\alpha$ , interferon-gamma, and malondialdehyde were also observed to be reduced. The oligopeptides increased the serum levels of superoxide dismutase and glutathione.<sup>2</sup> Similarly, through in vitro evaluation, bioactive peptides have been observed to decrease the generation of cytokines, IL-1 $\beta$  and TNF- $\alpha$ , when pancreatic  $\beta$ -cells are exposed to high glucose, suggesting that damage or apoptosis of pancreatic  $\beta$ -cells can be prevented from diabetic-induced oxidative stress.<sup>48</sup> Marine collagen isolated from fish was shown not only to regulate metabolic nuclear receptors but also reduce free fatty acids in T2DM patients with or without hypertension.<sup>82</sup> Undigested Goby fish (*Zosterisessor ophiocephalus*) muscle protein and their hydrolysates administered to HFHD-induced oxidative stress rats can manage hyperglycaemia, restore the status of antioxidant, and ameliorate renal damage.<sup>83</sup> A milk-derived bioactive peptide,  $\beta$ -casomorphin-7, also acts as an antioxidant<sup>84</sup> by reducing the blood glucose level in the streptozotocin-induced diabetic rat.

Common bean peptides too can upregulate insulin-like growth factor 2 (IGF-II), alleviate obesity-associated insulin resistance, and contribute in anti-inflammation.<sup>85</sup> Rice bran and soybean flour are the example plant proteins that possess DPP-IV inhibitory activity.<sup>86,87</sup> Nutripeptin<sup>®</sup> and Hydro MN Peptide<sup>®</sup> are marine protein hydrolysates that are effective in reducing the post-prandial blood glucose level and managing T2DM symptoms.<sup>88</sup> Evidence of lowering both blood glucose and HbA1c levels was shown by the use of cholera toxin B sub-unit and the use of an active peptide derived from shark liver (CTB-APSL) fusion protein through.<sup>7</sup> It also can promote the secretion of insulin and enhance insulin resistance. Recently, anti-diabetic enzymatic protein hydrolysates and peptides have been gaining interest. Suetsuna and Saito showed that hypoglycaemic activity became apparent from isolated *Porphyra yezoensis* when boiled laver mixture hydrolysate fractions were decomposed by pepsin.<sup>89</sup> Similarly, Harnedy and FitzGerald reported precursors for generation of peptides which possessed DPP IV inhibitory activity from 3 hydrolysed fractions of *Palmaria palmata* protein.<sup>35</sup>

## Sulphated Polysaccharide

Sulphated polysaccharide isolated from *Cymodocea nodosa* (CNSP) inhibited  $\alpha$ -amylase activity and reduced the blood glucose level by protecting pancreatic  $\beta$ -cells.<sup>90</sup> It can also increase the insulin secretion in the blood, leading to improved metabolism and body weight.<sup>90</sup> In addition, CNSP also prevents the conversion of starch to simple sugars by inhibiting the enzyme responsible in the conversion process.<sup>90</sup> Hypoglycaemic effect is present due to the stimulation of Langerhans islets,

**Table 8** Macroalgae *Sargassum confusum*-Derived Pigment and Their Anti-Diabetic Potential

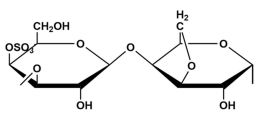
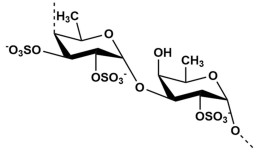
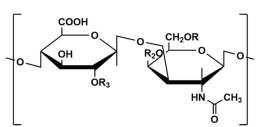
| Species                   | Compound/ Extract | Structure | Mechanism of Action  | Reference |
|---------------------------|-------------------|-----------|--|-----------|
| <i>Sargassum confusum</i> | Oligosaccharides  | na        | Regulation of insulin receptor substrate 1/phosphatidylinositol 3-kinase<br>Regulation of c-Jun N-terminal kinase pathways | [79]      |

the enhancement of insulin sensitivity, and strong antioxidant effect. Polysaccharides contain the hydroxyl (OH) functional group, which may facilitate glucose binding leading to reduced blood glucose level. In a study conducted by Li et al, administration of marine polysaccharides reduced blood glucose level and exhibited a high antioxidant activity.<sup>91</sup> Wijesekara et al reported that sulphated polysaccharides possessed anti-diabetic activity and antioxidant activity demonstrating its effectiveness in reducing blood glucose level.<sup>92</sup> Huang et al reported that sulphated polysaccharides possess anti-diabetic activity that can lead to weight gain and glycaemic regulation.<sup>93</sup> Carrageenan isolated from a red seaweed, *Kappaphycus alvarezii*, elicits its anti-diabetic activity through  $\alpha$ -glucosidase inhibition.<sup>94</sup> The soluble fibre present in carrageenan reduces the amount of carbohydrates reaching the bloodstream by slowing down the absorption in the small intestine.<sup>66</sup> Presence of free radicals in the body can trigger the development of diabetes. Sulphated polysaccharides have protective effect against oxidative stress due to the presence of natural antioxidants and, hence, demonstrate their potential as a therapy for DM.<sup>95</sup> Table 9 highlights some marine-derived polysaccharides with anti-diabetic potential.

## Chromium (III) Derivatives

Chromium (III) is a common metal which can be used as a nutritional supplement for T2DM patients.<sup>99</sup> It stimulates glucose metabolism by promoting insulin activity in the peripheral tissue. Similarly, the action of chromium directly affects insulin receptors and the affinity towards insulin.<sup>100</sup> It also involves phosphorylation that leads to the modulation of signal multiplying protein.<sup>100</sup> Polysaccharide chromium (III) derivative has gained much importance in improving T2DM. Chromium supplementation plays a major role in insulin-resistant animals as it potentiates the effect of insulin, enhances the PI3K/PKB insulin signalling pathways, and improves AMPK activity.<sup>101</sup> Sulphated polysaccharide isolated from *Enteromorpha prolifera* was used in the preparation of rhamnan-type sulphated polysaccharide derivatives (SPED) which was effective in enhancing glucose metabolism.<sup>102</sup> Polysaccharides-chromium (III) complex isolated from *Inonotus obliquus* enhanced the oral glucose tolerance test in mice with T2DM and showed that it could enhance the glucose tolerance capacity.<sup>99</sup> Moreover, SPED improves the insulin sensitivity by alleviating the pancreatic  $\beta$ -cell dysfunction<sup>103</sup> and ameliorates hyperglycaemia by increasing the production of hepatic glycogen in insulin-resistant mice.<sup>102</sup> In another study, *Enteromorpha prolifera* contains sulphated rhamnose polysaccharides, and a complex of sulphated rhamnose polysaccharides chromium (III) (SRPC) was

**Table 9** Marine-Derived Polysaccharides and Their Anti-Diabetic Potential

| Species                                  | Compound/Extract         | Structure  | Mechanism of Action  | Reference |
|--|--------------------------|--|--|-----------|
| <i>Cymodocea nodosa</i> (seagrass)       | Sulphated polysaccharide | na   | $\alpha$ -amylase inhibition   | [90]      |
| <i>Kappaphycus alvarezii</i> (seaweed)   | Carrageenan              |  | $\alpha$ -glucosidase inhibition   | [94]      |
| <i>Cucumaria frondose</i> (sea cucumber) | Fucoidan                 |  | <ul style="list-style-type: none"> <li><math>\alpha</math>-glucosidase inhibition</li> <li><math>\alpha</math>-amylase inhibition</li> </ul> | [96,97]   |
| <i>Urechis unicinctus</i> (worm)         | Glycosaminoglycan        |  | na   | [98]      |

synthesized. SRPC was found to possess hypoglycaemic effect, enhanced glucose tolerance, and improved insulin resistance in high-fat high-sucrose diet (HFSD)-induced T2DM mice.<sup>104</sup>

## Fucoidan

Fucoidan resembles heparin due to its highly sulphated skeleton and can be found in brown marine algae. Fucoidan exhibits  $\alpha$ -glucosidase and  $\alpha$ -amylase activity and can prevent incidence of DM by preventing oxidative stress.<sup>96,104</sup> It is more potent than other  $\alpha$ -D-glucosidase inhibitors such as acarbose with an  $IC_{50}$  range of 0.013–0.047 mg mL<sup>-1</sup>.<sup>97</sup> The inhibitory activities of fucoidan are affected by the structure and composition of the compound.<sup>97</sup> Fucoidan with a low molecular weight and high sulphate content is suitable for inhibitory activity against  $\alpha$ -amylase and  $\alpha$ -glucosidase activity.<sup>97</sup> Treatment with fucoidan in diabetic rats lowered blood glucose level and improved insulin sensitivity.<sup>105</sup> Administration of fucoidan can reduce the SOD activity and increase malondialdehyde (MDA) level and decrease in HbA1c levels.<sup>105</sup> On the other hand, fucoidan from sea cucumber *Cucumaria frondosa* normalized the PI3K/PKB pathway and GLUT4 translocation.<sup>106</sup> Hence, fucoidan may be a potential therapy for DM.

## Glycosaminoglycan

Glycosaminoglycan isolated from *Urechis unicinctus* reduced the blood glucose level, insulin resistance in homeostatic model assessment (HOMA-IR), and area under the curve in diabetic rats.<sup>98</sup> It also enhanced the glucose tolerance and eased the symptoms in the diabetic mice, suggesting glycosaminoglycan exhibits good anti-diabetic effect.<sup>98</sup> Glycosaminoglycan exhibits antioxidant effect by improving the glutathione peroxidase (GSH-Px) and SOD activity in the liver of diabetic mice and significantly reduces the concentration of MDA.<sup>98</sup> Glycosaminoglycan possesses hypoglycaemic activity and enhances the capacity of antioxidant by repairing pancreas and liver tissue.<sup>98</sup>

## Secondary Metabolites

### Bromophenols

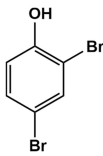
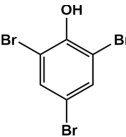
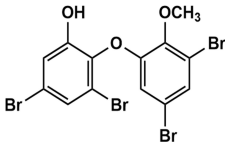
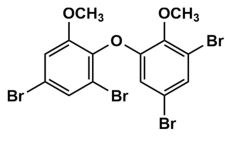
Bromophenols are compounds that exhibit numerous biological activities beneficial to human, and they can be found widely distributed in marine algae. Bromophenols isolated from marine algae demonstrate anti-diabetic potential through their antioxidant activity and inhibition of enzymes related to diabetes. Two bromophenols, 2,4-dibromophenol and 2,4,6-tribromophenol, isolated from a red alga, *Grateloupia elliptica*, exhibited potent  $\alpha$ -glucosidase inhibitory activity. These compounds also exhibited a mild inhibition against rat intestinal maltase ( $IC_{50}$  4.8 and 5.0 mM, respectively) and rat-intestinal sucrase ( $IC_{50}$  3.6 and 4.2 mM, respectively).<sup>31</sup> Another bromophenol, bis(2,3-dibromo-4,5-dihydroxybenzyl)ether (BDDE), isolated from *Polyopes lancifolia*, exhibited a strong  $\alpha$ -glucosidase inhibitory activity.<sup>107</sup> Liu et al investigated the BDDE- $\alpha$ -glucosidase inhibitory mechanism. It was observed that the  $\alpha$ -glucosidase enzyme changes conformation when synthetic BDDE is attached to it. The study suggested that BDDE- $\alpha$ -glucosidase interaction was driven by both hydrogen bonds and hydrophobic forces.<sup>108</sup> Kurihara et al found that inhibitory potencies of bromophenol could be enhanced by lowering the degree of methyl substitution and elevating the degree of bromo substitution per benzene ring.<sup>109</sup> Hence, these findings could be a stepping stone for developing novel  $\alpha$ -glucosidase inhibitors for effective treatment of diabetes.<sup>108</sup> Apart from being a potent  $\alpha$ -glucosidase inhibitor, BDDE can also elevate the glucose uptake in insulin-resistant HepG2 cells. In addition, in vivo study evidenced that BDDE remarkably lowered the blood glucose, triglyceride, and glycosylated haemoglobin (HbA1c) levels. It also activated the phosphorylation of IR- $\beta$  in gastrocnemii and decreased the expression of PTP1B. At high doses, BDDE reduced the body weight without affecting both water and food intake.<sup>110</sup>

The bromophenols 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether, bis(2,3,6-tribromo-4,5-dihydroxyphenyl)-methane and 1,2-bis(2,3,6-tribromo-4,5-dihydroxyphenyl)-ethane isolated from *Symphycloadia latiuscula*, a species of marine red alga, demonstrated a high PTP1B inhibitory activity with  $IC_{50}$  values of 3.9, 4.3, and 3.5  $\mu$ mol L<sup>-1</sup>, respectively.<sup>111</sup> Another four bromophenol derivatives, 2,2',3,3'-tetrabromo-4,4',5,5'-tetra-hydroxydiphenyl methane, 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl) pyrocatechol, bis(2,3-dibromo-4,5-dihydroxybenzyl)-ether and 2,2',3-tribromo-3',4,4',5-tetrahydroxy-6'-ethyloxy-methyl diphenylmethane isolated from ethanolic extract from red alga, *Rhodomela confervoides*, showed in vivo anti-hyperglycaemic potential believed to be partially attributed to their strong PTP1B inhibitory activities.<sup>112</sup> In a study by

Shi et al three bromophenols, 3,4-dibromo-5-(methoxymethyl)-1,2-benzenediol, 2-methyl-3-(2,3-dibromo-4,5-dihydroxy)-propylaldehyde, and 3-(2,3-dibromo-4,5-dihydroxy-phenyl)-4-bromo-5,6-dihydroxy-1,3-dihydroiso-benzofuran isolated from *R. confervoides* exhibited potent inhibitory activity against PTP1B.<sup>113</sup> In an in vivo study, 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(isopropoxymethyl)benzyl)-benzene-1,2-diol (HPN), a synthetic analogue of bromophenol also isolated from *R. confervoides*, showed significant reduction in serum blood glucose ( $P < 0.01$ ) after eight weeks of treatment. In addition, HPN was also found to decrease serum triglycerides and total cholesterol concentration in a dose-dependent manner. Moreover, HPN also significantly reduced the HbA1c levels ( $P < 0.05$ ) in medium- and high-dose group. There was a reduction in the PTP1B levels in pancreatic tissue, and the intraperitoneal glucose tolerance test in rats showed HPN exhibits a blood lowering activity like rosiglitazone.<sup>43</sup> Another two bromophenols, 3',5',6',6-tetrabromo-2,4-dimethyldiphenyl ether and 2',5',6',5,6-pentabromo-3',4',3,4-tetramethoxybenzo-phenone isolated from *Laurencia similis* demonstrated potent PTP1B inhibitory activities with  $IC_{50}$  values of 2.97 and 2.66  $\mu\text{M}$ , respectively.<sup>114</sup> These are also shown in Table 3.

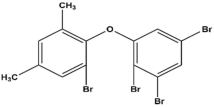
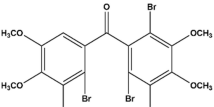
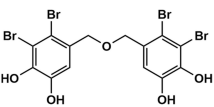
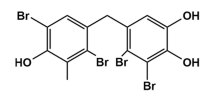
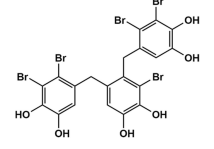
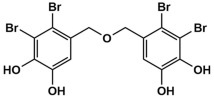
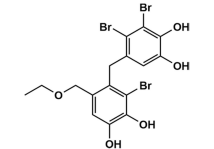
A methyl derivative of the sole bioactive component of *Lamellodysidea herbacea* strongly inhibits PTP1B ( $IC_{50}$  1.7  $\mu\text{M}$ ) with no apparent cytotoxicity.<sup>115</sup> A synthetic highly brominated compound derived from bromophenol isolated from *R. confervoides* demonstrated a promising PTP1B inhibitory activity and a propitious in vivo anti-diabetic activity.<sup>116</sup> Bromophenols isolated from *Symphyclocladia latiuscula*, especially the highly brominated agents, may represent novel anti-diabetic drugs as they inhibit both PTP1B and  $\alpha$ -glucosidase as well as having the ability to enhance the glucose uptake and insulin sensitivity.<sup>117</sup> Table 10 compiles the marine-derived bromophenols and their anti-diabetic potentials.

**Table 10** Marine-Derived Bromophenols Possessing Anti-Diabetic Potential

| Species                                      | Compound/Extract                                   | Structure   | Mechanism of Action   | Reference |
|--|--|---|---|-----------|
| <i>Grateloupia elliptica</i><br>(macroalgae) | 2,4-dibromophenol                                  |   | $\alpha$ -glucosidase inhibition<br>intestinal sucrase inhibition<br>maltase inhibition | [31]      |
|  | 2,4,6-tribromophenol                               |  |   |           |
| <i>Lamellodysidea herbacea</i><br>(sponge)   | Polybromodiphenyl ether                            |  | PTP1B inhibition  | [115]     |
|  | Methyl ether derivative of polybromodiphenyl ether |  |   |           |

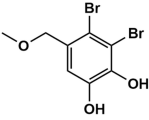
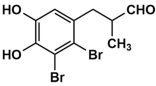
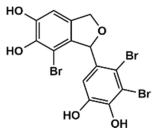
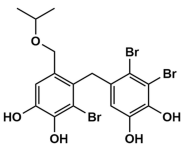
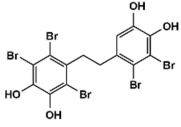
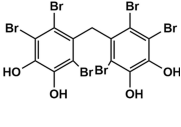
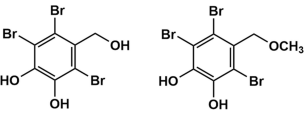
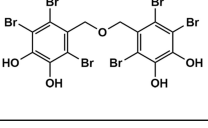
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Table 10 (Continued).

| Species                                      | Compound/Extract   | Structure   | Mechanism of Action   | Reference        |
|--|--|---|---|------------------|
| <i>Laurencia similis</i><br>(macroalgae)     | 3',5',6',6-tetrabromo-2,4-dimethyldiphenyl ether                         |    | PTPIB inhibition  | [114]            |
|  | 2',5',6',5,6-pentabromo-3',4',3,4-tetramethoxybenzo-phenone              |    |   |                  |
| <i>Polyopes lancifolia</i><br>(macroalgae)   | bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (BDDE)                        |    | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• intestinal sucrase maltase inhibition</li> <li>• PTPIB inhibition</li> </ul> | [107,110]        |
| <i>Rhodomela confervoide</i><br>(macroalgae) | 2,2',3,3'-tetrabromo-4,4',5,5'-tetrahydroxydiphenyl methane              |    | PTPIB inhibition  | [43,112,113,116] |
|  | 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl) pyrocatechol            |  |   |                  |
|  | bis-(2,3-dibromo-4,5-dihydroxybenzyl) ether                              |  |   |                  |
|  | 2,2',3-tribromo-3',4,4',5-tetrahydroxy-6'-ethoxy- methylidiphenylmethane |  |   |                  |

(Continued)

Table 10 (Continued).

| Species  | Compound/Extract  | Structure   | Mechanism of Action   | Reference |
|--|---|---|---|-----------|
|  | 3,4-dibromo-5-(methoxymethyl)-1,2-benzenediol   |    |   |           |
|  | 2-methyl-3-(2,3-dibromo-4,5-dihydroxy)-propylaldehyde                                       |    |   |           |
|  | 3-(2,3-dibromo-4,5-dihydroxy-phenyl)-4-bromo-5,6-dihydroxy-1,3-dihydroiso-benzofuran        |    |   |           |
|  | 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(isopropoxymethyl)benzyl)benzene-1,2-diol (HPN)      |   |   |           |
| <i>Symphyclocladia latiuscula</i> (macroalgae) | 1,2-bis(2,3,6-tribromo-4,5-dihydroxyphenyl)-ethane  |  | PTPIB inhibition  | [117]     |
|  | bis(2,3,6-tribromo-4,5-dihydroxyphenyl) methane   |  | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• Enhance glucose uptake</li> <li>• PTPIB inhibition</li> <li>• Enhance insulin sensitivity</li> </ul> |           |
|  | 2,3,6-tribromo-4,5-dihydroxybenzyl alcohol, 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether |  |   |           |
|  | bis-(2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether)                                       |  |   |           |

**Abbreviation:** TPIB, protein tyrosine phosphatase-1B.

## Carboxylic Acid

Phthalic acid, a potent bioactive compound, isolated from ascidian *Phallusia nigra*, was investigated for T2DM activity (Table 11). The results from the docking studies and data analysis had indicated that phthalic acid demonstrated a prominent anti-diabetic effect compared to fidarestat.<sup>118</sup>

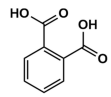
## Butenolide Derivatives

Three butenolide derivatives (2,3-disubstituted disubstituted  $\gamma$ -butenolide), namely flavipesolide A, flavipesolide B, and flavipesolide C, were isolated from *Aspergillus flavipes* HN4-13 along with several other inactive butenolide derivatives.<sup>119</sup> Although all the three butenolide derivatives act as strong  $\alpha$ -glucosidase inhibitors, flavipesolide A and B are more potent than flavipesolide C.<sup>119</sup> The butenolide derivatives phenyl- and benzyldisubstituted  $\gamma$ -butenolide isolated from a coral-associated fungus *Aspergillus* sp. showed  $\alpha$ -glucosidase inhibition activity.<sup>120</sup> Table 12 compiles the marine-derived butenolide derivatives and their anti-diabetic potentials.

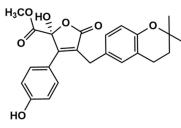
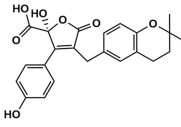
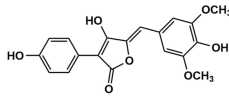
## Carotenoids

Hosokawa et al proposed that carotenoids exhibit anti-diabetic activities.<sup>121</sup> Carotenoids such as fucoxanthin and astaxanthin possess strong anti-diabetic activity.<sup>122</sup> Fucoxanthin is generally found in macroalgae such as *Eisenia bicyclis* and *Undaria pinnatifida* that have brown complexion. In an animal study, glucose levels and insulin levels in the plasma were found to be reduced when fucoxanthin was introduced.<sup>122</sup> Rats administered with a diet consisting of fucoxanthin (0.2%) indirectly reduced insulin resistance. Maeda et al proposed that this reduction was due to suppression of TNF- $\alpha$

**Table 11** Marine-Derived Carboxylic Acid Having Anti-Diabetic Potential

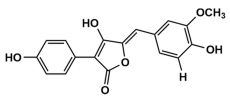
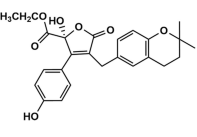
| Species                           | Compound/Extract | Structure  | Mechanism of Action         | Reference |
|-----------------------------------|------------------|--|-----------------------------|-----------|
| <i>Phallusia nigra</i> (Tunicate) | Phthalic acid    |  | Aldose reductase inhibition | [118]     |

**Table 12** Microbial-Derived Butenolide Derivatives Possessing Anti-Diabetic Potential

| Species                     | Compound/Extract | Structure  | Mechanism of Action              | Reference |
|-----------------------------|------------------|--|----------------------------------|-----------|
| <i>Aspergillus flavipes</i> | Flavipesolide A  |   | $\alpha$ -glucosidase inhibition | [119]     |
|                             | Flavipesolide B  |   |                                  |           |
|                             | Flavipesolide C  |  |                                  |           |

(Continued)

Table 12 (Continued).

| Species                | Compound/Extract                          | Structure   | Mechanism of Action | Reference |
|------------------------|---|---|---------------------|-----------|
| <i>Aspergillus</i> sp. | Phenyl-disubstituted $\gamma$ -butenolide |  | na                  | [120]     |
|                        | Benzyl-disubstituted $\gamma$ -butenolide |  |                     |           |

mRNA and levels of plasma leptin.<sup>123</sup> Fucoxanthin supplementation also successfully decreased glucose and HbA1c levels as well as insulin in the plasma.<sup>124</sup> D’Orazio et al proposed that diabetes can be prevented using fucoxanthin. The diabetic mice undergo mRNA downregulation of various inflammatory mediators like tumour necrosis factor and interleukins, which is known to increase the glucose levels in the blood through upregulation of Glut4.<sup>12</sup> Similarly, Jung et al proposed that fucoxanthin can also act as advanced glycation end-products (AGE) inhibitor and PTP1B inhibitor.<sup>125</sup> As AGE accumulate in the body, diabetes and its complications tend to manifest.<sup>126</sup> Thus, owing to its AGE and PTP1B inhibitory properties, fucoxanthin displays a promising potential as a therapeutic agent for diabetes and its associated complications.<sup>125</sup> Astaxanthin can be a therapeutic agent in diabetics due to its high antioxidant and anti-glycative abilities.<sup>127</sup> It also can be used as a preventive agent for diabetics suffering from diabetic retinopathy and other diseases like macular degeneration.<sup>128</sup> Astaxanthin (50 mg kg<sup>-1</sup> day<sup>-1</sup>) administered in rats for 18 weeks lowered the fasting blood glucose compared to control group.<sup>122</sup> Arunkumar et al proposed that astaxanthin (6 mg kg<sup>-1</sup> day<sup>-1</sup>) in mice can enhance the insulin signalling through the beta receptor activation which simultaneously leads to greater release of reactive oxygen species and pro-inflammatory mediators like cytokines.<sup>129</sup> It has been observed that 20 mg<sup>-1</sup> kg<sup>-1</sup> b.w. of astaxanthin can be administered in alloxane-induced diabetic rats, continuously for 7 days, which can normally bring down the catalase, superoxide dismutase, and glutathione peroxidase activity in saliva.<sup>122</sup>

The changes in the antioxidant system of the saliva shows that astaxanthin has potential enough for treating diabetes.<sup>122</sup> Extract of *Chlorella zofingiensis*, a microalga, contains different content of astaxanthin. The extract rich in astaxanthin demonstrated higher antioxidant abilities and greater anti-glycative capacities, including the inhibition of AGEs formation, glucose autoxidation, as well as glycation-induced protein oxidation.<sup>56</sup> Intraperitoneal glucose tolerance test of astaxanthin treatment indicated it could preserve the islet cells’ function to secrete insulin.<sup>130</sup> Hence, astaxanthin can be an alternative therapeutic agent for diabetes. The marine-derived carotenoids are listed in Table 13.

## Furan

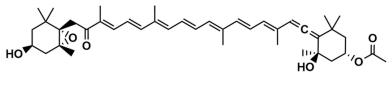
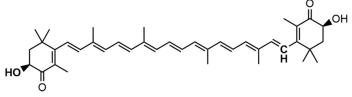
Hyrriosal, isolated from *Hyrrios erectus*, a marine sponge, possessed a dose-dependent non-competitive inhibitory effect against PTP1B (IC<sub>50</sub> 42  $\mu$ M). It also demonstrated extensive cellular effects on glucose transport, PI3K/AKT activation, and TGFbeta/Smad2 signalling. Additionally, hyrtiosal potentially showed that a potent amount can completely abolish the AKT translocation of the membrane. In fact, Glut4 in overexpressed PTP1B CHO cells was enhanced by increasing Glut4, and modulation of the insulin-mediated inhibition was activated via Smad2. Thus, the study suggested that further research could be carried out on hyrtiosal to establish its potential in treating diabetes.<sup>131</sup> Table 14 shows the structure of hyrtiosal.

## Macrolide

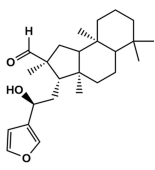
The macrolide des-O-methylsiodiplodin, isolated from *Cerbera manghas*, has the potential ability to reduce the blood glucose levels and HbA1c in mice. The in vivo results also showed that it rectified the pro-inflammatory factor and genes related to ROS expressions.<sup>132</sup> Marine-derived epoxykukalide possesses the ability to induce the replication of  $\beta$ -cells. It



**Table 13** Algal-Derived Carotenoids Having Anti-Diabetic Potential

| Species  | Compound/Extract | Structure   | Mechanism of Action   | Reference |
|--|------------------|---|---|-----------|
| <i>Eisenia bicyclis</i> , <i>Undaria pinnatifida</i> | Fucoanthin       |  | <ul style="list-style-type: none"> <li>Advanced glycation end-products (AGE) inhibitor</li> <li>Protein tyrosine phosphate 1B (PTP1B) inhibitor</li> </ul>  | [125]     |
| <i>Chlorella zofingiensis</i>                        | Astaxanthin      |  | <ul style="list-style-type: none"> <li>Advanced glycation end-products (AGE) inhibitor</li> <li>Preserve <math>\beta</math>-islet cells function</li> </ul> | [56]      |

**Table 14** Anti-Diabetic Hyrtiosal, Isolated from the Marine Sponge *Hyrtios erectus*

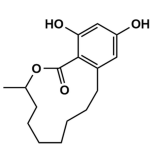
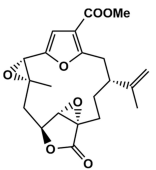
| Species                | Compound/Extract | Structure   | Mechanism of Action | Reference |
|------------------------|------------------|---|---------------------|-----------|
| <i>Hyrtios erectus</i> | Hyrtiosal        |  | PTP1B inhibition    | [131]     |

enhanced the  $\beta$ -cell proliferation and activation 2.5-fold through the ERK1/2 signalling pathway, and upregulations of cyclin D2 and cyclin E simultaneously happened. Furthermore, epoxy pukalide has demonstrated a protective role via basal and cytokine-mediated  $\beta$ -cell apoptosis in the islets. Thus, epoxy pukalide may serve as a new therapeutic for diabetes.<sup>133</sup> The marine-derived macrolides are exhibited in Table 15.

## Plastoquinones

Plastoquinones such as sargahydroquinonic acid, sargachromenol, and sargaquinonic acid isolated from *Sargassum serratifolium* have potential as a therapy for T2DM.<sup>134</sup> Although all these plastoquinones exhibit PTP1B inhibitory

**Table 15** Marine-Derived Glycolipids Having Anti-Diabetic Potential

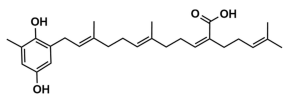
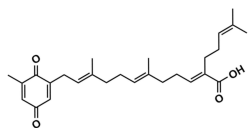
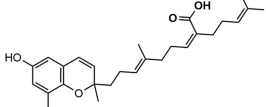
| Species                | Compound/Extract        | Structure   | Mechanism of Action  | Reference |
|------------------------|-------------------------|---|--|-----------|
| <i>Cerbera manghas</i> | des-O-methylsiodiplodin |  | Ameliorating the expression of obesity-related pro-inflammatory cytokines  | [132]     |
| Soft coral             | Epoxy pukalide          |  | <ul style="list-style-type: none"> <li>Increase <math>\beta</math>-cell proliferation through the ERK1/2 signalling pathway activation</li> <li>Cyclin D2 upregulations</li> <li>Cyclin E upregulations</li> </ul> | [133]     |

activity, it has been found that two compounds, namely sargachromenol and sargaquinoic acid, also exhibit inhibition of  $\alpha$ -glucosidase enzyme.<sup>134</sup> Sargahydroquinoic acid and sargaquinoic acid activate both PPAR $\alpha$  and PPAR $\gamma$  and, thereby, enhance the metabolic disorders without the side effects such as weight gain and renal failure observed in the previous PPAR agonists.<sup>135</sup> Among the three plastoquinones, sargachromenol showed the best  $\alpha$ -glucosidase inhibition, followed by sargaquinoic acid, while sargahydroquinoic acid was inactive.<sup>136</sup> Kim et al identified *Sargassum yezoense*-derived dual agonists sargaquinoic acid (SQA) and sargahydroquinoic acid (SHQA), where SQA demonstrated a stronger binding affinity with PPAR $\gamma$  compared to specific PPAR $\gamma$  agonist, troglitazone, which eventually activated PPAR $\gamma$  transcriptional activity. In addition, SQA- and SHQA-treated 3T3-L1 cells caused an increase in differentiation of adipocyte and elevated expression of PPAR $\gamma$ , aP2, adiponectin, resistin, Glut4, and C/EBP $\alpha$ . Hence, the study results suggested that both SQA and SHQA could be used to decrease the insulin resistance through adipogenesis regulation.<sup>137</sup> Table 16 lists the marine-derived anti-diabetic plastoquinones.

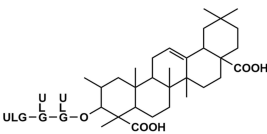
## Saponins

The anti-diabetic activity of saponins is observed due to the atrophy of beta cells that leads to enhanced insulin secretion and glycogen in the liver<sup>138</sup> (Table 17). When diabetic rats were compared to that of the healthy ones, decreased glucose levels, increased insulin levels comparative to healthy ones are obtained.<sup>139</sup> Decrease in blood

**Table 16** Macroalgal-Derived Anti-Diabetic Plastoquinones and Their Mechanism of Action

| Species  | Compound/Extract       | Structure  | Mechanism of Action   | Reference |
|--|------------------------|--|---|-----------|
| <i>Sargassum serratifolium</i> , <i>Sargassum yezoense</i> | Sargahydroquinoic acid |   | <ul style="list-style-type: none"> <li>• PTP1B inhibitory</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• PPAR<math>\alpha</math>/PPAR<math>\gamma</math> dual agonists</li> </ul> | [134,137] |
|  | Sargaquinoic acid      |   |   |           |
| <i>Sargassum serratifolium</i>                             | Sargachromenol         |  | <ul style="list-style-type: none"> <li>• PTP1B inhibitory</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• PPAR<math>\alpha</math>/PPAR<math>\gamma</math> dual agonists</li> </ul> | [134,137] |

**Table 17** Invertebrate-Derived Saponins and Their Anti-Diabetic Potential

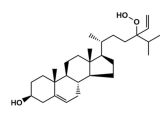
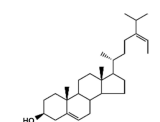
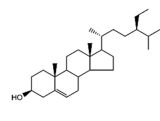
| Species                   | Compound/Extract | Structure   | Mechanism of Action   | Reference |
|---------------------------|------------------|---|---|-----------|
| <i>Holothuria thomasi</i> | Saponins         |  | <ul style="list-style-type: none"> <li>• Intestinal <math>\alpha</math>-glucosidase inhibition</li> <li>• Pancreatic <math>\alpha</math>-amylase inhibition activity</li> </ul> | [143]     |

glucose levels generally occurs through varied pathways which lead to inhibition of glucose in the blood.<sup>140–142</sup> The saponin-treated groups showed reduction in the  $\alpha$ -amylase exhibiting as intestinal  $\alpha$ -glucosidase and pancreatic  $\alpha$ -amylase inhibitory activity.<sup>143</sup> The presence of antioxidants in saponin can reduce oxidative stress related to the incidence of DM. In a study, diabetic rats treated with saponin had reduced serum IL-6 and TNF- $\alpha$  concentrations.<sup>139</sup> Ginsenosides saponins can hinder the lipopolysaccharide-induced generation of TNF- $\alpha$  by inhibiting the transcription factor of nuclear factor kappa light-chain enhancer of activated B cells (NF- $\kappa$ B) through which the regulation of transcription of many genes related to inflammation occurs.<sup>144</sup> Saponin possesses antioxidant activity as liver L-MDA was reduced upon its administration.<sup>145</sup> The level of antioxidant enzymes such as SOD and CAT also improved.<sup>145</sup> Saponin may have a functional ROS-protective mechanism that can help regenerate pancreatic  $\beta$ -cells and prevent the destruction of pancreatic islets from alloxan cytotoxic effects.<sup>145</sup> In addition, saponin is a good metals chelator.<sup>145</sup> The OH groups in the saponin increase antioxidant activity and prevent the formation of ROS.

## Sterols

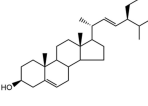
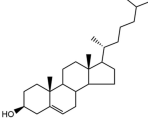
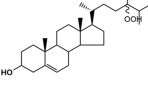
Six different sterols, namely 24(S)-hydroxy-24-vinylcholesterol, fucosterol, 24(R)-hydroxy-24-vinylcholesterol,  $\beta$ -sitosterol, stigmasterol, and cholesterol, were isolated from *Sargassum glaucescens* and investigated for their anti-diabetic potential. In vitro  $\alpha$ -amylase inhibitory test revealed a potent inhibition of the enzyme which was higher compared to acarbose (IC<sub>50</sub> value  $8.9 \pm 2.4$  mg mL<sup>-1</sup>).<sup>146</sup> An in vivo study showed that oral administration of fucosterol (30 mg kg<sup>-1</sup>) isolated from *Pelvetia siliquosa* caused a prominent reduction in serum glucose concentrations and inhibited accumulation of sorbitol in lenses. The study concluded that fucosterol was a main contributor of anti-diabetic property in *P. siliquosa*.<sup>147</sup> The promising application in treating diabetes is observed in the study which revealed that fucosterol exhibits aldose reductase inhibitory activity. Additionally, the study demonstrated that fucosterol inhibited PTP1B non-competitively.<sup>148</sup> Thus, fucosterol can potentially be used as anti-diabetic agent. The sterols highlighted are shown in Table 18.

**Table 18** Macroalgae-Derived Sterols and Their Anti-Diabetic Potential

| Species                      | Compound/Extract                  | Structure  | Mechanism of Action            | Reference |
|------------------------------|-----------------------------------|--|--------------------------------|-----------|
| <i>Sargassum glaucescens</i> | 24(S)-hydroxy-24-vinylcholesterol |  | ● $\alpha$ -amylase inhibition | [146]     |
|                              | 24(R)-hydroxy-24-vinylcholesterol |  |                                |           |
|                              | $\beta$ -sitosterol               |  |                                |           |

(Continued)

Table 18 (Continued).

| Species  | Compound/Extract | Structure   | Mechanism of Action  | Reference |
|--|------------------|---|--|-----------|
|  | Stigmasterol     |  |  |           |
|  | Cholesterol      |  |  |           |
| <i>Sargassum glaucescens</i> , <i>Pelvetia siliquosa</i> | Fucosterol       |  | <ul style="list-style-type: none"> <li>• RLAR inhibition</li> <li>• HRAR inhibition</li> <li>• PTP1B inhibition</li> </ul> | [147]     |

## Tannins

Marine algae-derived phlorotannin is extensively studied for its anti-diabetic potential due to various mechanisms like PTP1B,  $\alpha$ -amylase, and  $\alpha$ -glucosidase inhibitory activity, glucose utilizing effect in skeletal muscle, insulin sensitivity improvement in T2D db/db mice, and provides protection against diabetes complication.<sup>149</sup> Phlorotannin-rich extract of *Ascophyllum*, an edible marine macroalga, was found to be effective in inhibiting  $\alpha$ -glucosidase at low levels with an  $IC_{50}$  20  $\mu\text{g mL}^{-1}$  GAE.<sup>32</sup> An in vivo study confirmed the ability of phlorotannin extracts to lower the normal rise in post-prandial blood glucose by 90% and to decrease peak secretion of insulin by 40%.<sup>150</sup> Moon et al isolated 6 different phlorotannins from two edible marine algae, *Eisenia bicyclis* and *Ecklonia stolonifera*. The compounds eckol, phlorofurofuceckol-A, dieckol, and 7-phloroeckol were potent PTP1B inhibitors with  $IC_{50}$  values ranging from 0.56 to 2.64  $\mu\text{M}$ , and they inhibited PTP1B non-competitively. With  $IC_{50}$  values ranging from 1.37 to 6.13  $\mu\text{M}$ , phlorofurofuceckol-A, dieckol, and 7-phloroeckol were considered to have the most potent  $\alpha$ -glucosidase activity.<sup>151</sup>

Phlorotannins isolated from *Eisenia bicyclis*, fucofuroeckol A, and dioxinodehydroeckol showed significant  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory activity.<sup>152</sup> The in vivo study reveals that phlorotannin-rich methanolic extract of *E. stolonifera* demonstrated anti-hyperglycaemic effect and brought about decrease in lipid peroxidation in unfasted KK-Ay mice in a dose-dependent manner.<sup>153</sup> A phlorotannin-rich Alaskan seaweed demonstrated  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory activities with potential in limiting the sugar release from carbohydrate and, thus, alleviating the post-prandial hyperglycaemia.<sup>154</sup> Three phlorotannins isolated from *Ecklonia maxima* were observed to have antioxidant effect on DPPH free radicals, and two of them, dibenzo-1,4-dioxin-2,4,7,9-tetraol and hexahydroxyphenoxydibenzo-1,4-dioxin, possessed more potent  $\alpha$ -glucosidase inhibitory activity and antioxidant effect than positive controls.<sup>155</sup> Phlorotannins exhibit prominent inhibitory activity against AGE, rat lens aldose reductase (RLAR), angiotensin converting enzyme (ACE), peroxynitrite, and reactive oxygen species (ROS).<sup>156</sup>

A seaweed-derived phlorotannin, diphlorethohydroxycarmalol (DPHC), possesses a protective effect against oxidative stress which is induced by hyperglycaemia as it significantly inhibited high glucose-induced toxicity and apoptosis. It decreased both thiobarbituric acid-reactive substrates (TBARS) and ROS generation and elevated nitric oxide level induced by glucose while increasing the activities of antioxidant enzymes.<sup>157</sup> In addition, DPHC suppressed the over-expression of COX-2 proteins, inducible nitric oxide synthase (iNOS), and NF- $\kappa$ B activation induced by glucose.<sup>158</sup> As stated by Heo et al, *Ishige okamurae*-derived DPHC showed significant  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory activities

with  $IC_{50}$  values of 0.16 and 0.53 mM, respectively, which reflected more potent effects than acarbose.<sup>159</sup> According to Fernando et al, treatment with DPHC suppressed the dilation in retinal diameter and vessel formation induced by high glucose. It inhibited expression of high glucose-induced vascular endothelial growth factor receptor 2 and its signalling cascade. Hence, it was concluded to be potential therapy against diabetic-induced angiogenesis.<sup>160</sup>

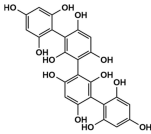
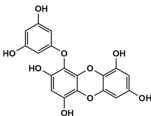
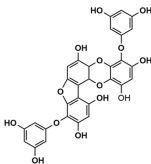
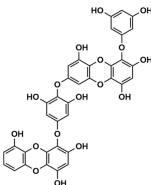
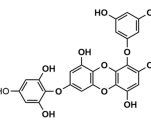
Octaphloretol A (OPA), a phlorotannin isolated from *Ishige foliacea*, is reported to have anti-diabetic potential. Lee et al found OPA to increase the uptake of glucose in differentiated L6 rat myoblast cells dose-dependently relative to control. It also increased Glut4 translocation to the plasma membrane which was mediated by PI3-K/Akt and AMPK activation.<sup>161</sup> Lee et al discovered that OPA had a higher  $\alpha$ -glucosidase inhibitory activity compared to acarbose ( $IC_{50}$  0.11 mM). Molecular modelling studies indicated that OPA interacted with Arg526, Asp542, Asp203, His600, Lys480, Met444, Phe450, Phe575, Ser448, and Tyr605. As compared to normal, OPA significantly suppressed the increase in post-prandial blood glucose levels in the diabetic mice.<sup>162</sup> Apart from its anti-diabetic effects, Lee et al also reported the in vivo antioxidant activity of OPA showing protective effect against all biochemical parameters studied. It also suppressed apoptosis and was associated with reductions in pro-apoptotic Bax and cleaved caspase-3 expressions and elevated anti-apoptotic BclxL expression.<sup>163</sup> Lee et al also concluded that the mechanism of OPA activity might involve the activation of AMPK which leads to glucose uptake in skeletal muscle through Glut4-mediated and inhibition of PEPCK and G6Pase activity in the liver leading to the suppression of gluconeogenesis. Thus, the findings provide a new opportunity through the clinical application of OPA as a potential anti-diabetic agent.<sup>18</sup>

Phloroglucinol was also one of the phlorotannins that could be potentially used as therapeutic for diabetes. Phloroglucinol, isolated from the brown alga *Eisenia bicyclis*, inhibits glycation and  $\alpha$ -amylase.<sup>164</sup> Five phloroglucinol derivatives isolated from *Ecklonia cava* demonstrated evident  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory activity dose-dependently, with  $IC_{50}$  values at  $10.8 \mu\text{mol L}^{-1}$  and  $124.9 \mu\text{mol L}^{-1}$ , respectively.<sup>165</sup> In an in vivo study phloroglucinol exhibited protective effects against AGE formation which were generated in a non-enzymatic glycation process which is associated with ageing, diabetes, and other chronic illnesses.<sup>166</sup> A new phloroglucinol derivative, 2-(4-(3,5-dihydroxyphenoxy)-3,5-dihydroxyphenoxy)-benzene-1,3,5-triol (DDBT) isolated from *Sargassum patens*, showed a potent inhibitory activity against carbohydrate-hydrolysing enzymes anticipated to help in diabetes prevention.<sup>167</sup> Ishophloroglucin A isolated from *Ishige okamurae* was also found to exhibit the highest  $\alpha$ -glucosidase inhibitory effect.<sup>168</sup> Lee et al reported potent  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory activities of dieckol, a phloroglucinol derivative isolated from brown algae, *Ecklonia cava*, with an  $IC_{50}$  values of 0.24 and 0.66 mM, respectively, a more potent effect than acarbose. In vivo study showed suppression of post-prandial blood glucose levels after dieckol administration to diabetes-induced or normal mice.<sup>169</sup> Two years later, Lee et al conducted another in vivo study which showed that the animals fed with dieckol-rich extract (AG-dieckol) had significantly reduced glucose in the blood, plasma insulin levels were increased as well as HbA1c levels, while drastic improvement in glucose tolerance was also observed. In contrast to the control group, the AG-dieckol group had markedly reduced plasma and hepatic lipids concentration.<sup>170</sup> Consequently, a randomized double blind, placebo-controlled trial was conducted to investigate the safety and efficacy of AG-dieckol extract in humans. AG-dieckol supplementation decreased post-prandial glucose level compared to placebo after a period of 12 weeks. Nevertheless, no adverse effects were observed during the intervention period.<sup>171</sup>

Kang et al reported that intraperitoneal administration of dieckol to diabetes-induced animals significantly reduced body weight, blood glucose, and serum insulin level compared to the saline-administered group.<sup>172</sup> In addition, increased activities of antioxidant enzymes and reduction in TBARS were also observed. Western blotting analysis showed that phosphorylation levels of AMPK and Akt were elevated. The study concluded that dieckol is a potential therapeutic agent for diabetes.<sup>172</sup> Another study evidenced that dieckol protected rat insulinoma cells from damage due to hyperglycaemic condition due to the suppression of apoptosis related with increased expression of anti-apoptotic Bcl-2 and decreased expression of pro-apoptotic cleaved caspase.<sup>173</sup> Dieckol treatment also decreased the overexpression of proteins such as COX-2, inducible nitric oxide synthase (iNOS), and NF- $\kappa$ B which were often induced by high glucose condition.<sup>174</sup> Overall, the anti-diabetic effect of dieckol helped in improving insulin sensitivity<sup>175</sup> as well as plasma glucose and hepatic glucose metabolic regulation.<sup>176</sup> Another phlorotannin, 6,6'-bieckol (BEK), isolated from *Ecklonia cava*, inhibited cytotoxicity induced by high glucose level. It decreased the high glucose-induced TBARS, nitric oxide level, and ROS generation. It also lowered the overexpression of COX-2, inducible nitric oxide synthase (iNOS), and NF- $\kappa$ B. The study concluded that BEK had potential in preventing endothelial dysfunction related to diabetes and other

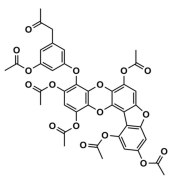
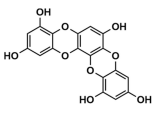
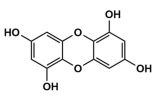

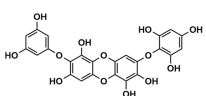
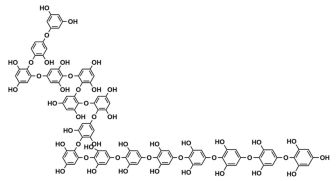
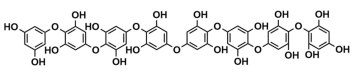
complications.<sup>177</sup> Phlorofucofuroeckol A isolated from the same alga also demonstrated higher inhibitory activities against  $\alpha$ -glucosidase and  $\alpha$ -amylase compared to acarbose with  $IC_{50}$  values of 19.52 and 6.34  $\mu$ M, respectively. Hence, it was a potent agent in alleviating post-prandial hyperglycaemia and had potential to be therapeutic as an anti-diabetic agent.<sup>178</sup> Table 19 contains a list of marine-derived tannins and their anti-diabetic mechanism of action.

**Table 19** Edible Macroalgae-Derived Tannins Possessing Anti-Diabetic Potential

| Species  | Compound/Extract      | Structure   | Mechanism of Action   | Reference        |
|--|-----------------------|---|---|------------------|
| Ascophyllum,<br>Alaskan<br>seaweed,<br><i>Ecklonia<br/>stolonifera</i> | Phlorotannins         |    | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• AGE, ACE, ROS inhibition</li> <li>• RLAR inhibition</li> <li>• Peroxynitrite inhibition</li> <li>• <math>\alpha</math>-amylase inhibition</li> </ul> | [32,153,154,156] |
| <i>Eisenia bicyclis</i> ,<br><i>Ecklonia<br/>stolonifera</i>           | Eckol                 |    | <ul style="list-style-type: none"> <li>• PTP1B inhibitory</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> </ul>  | [151]            |
|  | Phlorofucofuroeckol-A |   |   |                  |
|  | Dieckol               |  |   |                  |
| <i>Eisenia bicyclis</i> ,<br><i>Ecklonia<br/>stolonifera</i>           | 7-phloroeckol         |  | <ul style="list-style-type: none"> <li>• PTP1B inhibitory</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> </ul>  | [151]            |


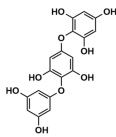
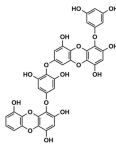
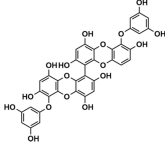
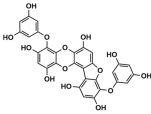
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Table 19 (Continued).

| Species                 | Compound/Extract                     | Structure  | Mechanism of Action   | Reference     |
|-------------------------|--------------------------------------|--|---|---------------|
| <i>Eisenia bicyclis</i> | Fucofuroeckol A (FF)                 |     | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• <math>\alpha</math>-amylase inhibition</li> </ul>  | [152]         |
|                         | Dioxinodehydroeckol (DD)             |     |   |               |
| <i>Ecklonia maxima</i>  | Dibenzo-1,4-dioxin-2,4,7,9-tetraol   |     | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• Antioxidant effect</li> </ul>  | [155]         |
|                         | Hexahydroxyphenoxydibenzo-1,4-dioxin |     |   |               |
| <i>Ishige okamuræ</i>   | Diphlorethohydroxycarmalol (DPHC)    |   | <ul style="list-style-type: none"> <li>• Antioxidant effect</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• <math>\alpha</math>-amylase inhibition</li> </ul>  | [157–160,168] |
|                         | Ishophloroglucin A                   |   | $\alpha$ -glucosidase inhibition  |               |
| <i>Ishige foliacea</i>  | Octaphlorethol A                     |  | <ul style="list-style-type: none"> <li>• Increase glucose in myoblast cells and translocation of Glut4 to the plasma membrane</li> <li>• Glucosidase inhibition</li> <li>• Antioxidant activity</li> <li>• Gluconeogenesis suppression</li> </ul> | [18,161–163]  |

(Continued)

Table 19 (Continued).

| Species                 | Compound/Extract   | Structure   | Mechanism of Action  | Reference |
|-------------------------|--|---|--|-----------|
| <i>Eisenia bicyclis</i> | Phloroglucinol   |    | <ul style="list-style-type: none"> <li>• Glycation</li> <li>• <math>\alpha</math>-amylase inhibition</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• Protective effect against AGE</li> </ul>   | [164–166] |
| <i>Sargassum patens</i> | 2-(4-(3,5-dihydroxyphenoxy)-3,5-dihydroxyphenoxy)-benzene-1,3,5-triol (DDBT) |    | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-amylase inhibition</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> </ul>   | [167]     |
| <i>Ecklonia cava</i>    |  |    | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-amylase inhibition</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> <li>• Antioxidant activity</li> </ul>   | [171,174] |
| <i>Ecklonia cava</i>    |  |   | <ul style="list-style-type: none"> <li>• Reduction of glucose-induced TBARS</li> <li>• Reduction of nitric oxide</li> <li>• Reduction of ROS generation</li> <li>• Downregulation of COX-2</li> <li>• Reduction of iNOS</li> <li>• Reduction of NF-<math>\kappa</math>B</li> </ul> | [177]     |
| <i>Ecklonia cava</i>    |  |  | <ul style="list-style-type: none"> <li>• <math>\alpha</math>-amylase inhibition</li> <li>• <math>\alpha</math>-glucosidase inhibition</li> </ul>   | [179]     |

## Terpenes

### Sesquiterpene

The sesquiterpene quinones purified from marine sponge *Dysidea* sp. have been evaluated for PTP1B inhibitory activity in vitro previously.<sup>180–182</sup> Li et al successfully isolated 21-dehydroxybolinaquinone, a new sesquiterpene quinone, along with two analogues, bolinaquinone and dysidine, from Hainan sponge *Dysidea villosa*. Among the analogues, dysidine appeared to have the most potent PTP1B inhibitory activity ( $IC_{50}$  6.70  $\mu$ M). Bolinaquinone which had a PTP1B inhibitory activity ( $IC_{50}$  5.45  $\mu$ M), also demonstrated cytotoxic activity against the HeLa cell line, whereas 21-dehydroxybolinaquinone moderately inhibited PTP1B ( $IC_{50}$  39.50  $\mu$ M) and demonstrated moderate cytotoxicity against the HeLa cell line ( $IC_{50}$  19.45  $\mu$ M).<sup>180</sup> In a study by Zhang et al, dysidine exhibited insulin-sensitizing activity, which increases the glucose uptake in 3T3-L1 cells as well as effectively activating the insulin pathway wherein its specific inhibitory activity against PTP1B could have played a role. Hence, dysidine could be a potential lead compound in



developing alternative adjuvant to insulin therapy.<sup>181</sup> Another sesquiterpene, dehydroeuryspongin A, isolated from the sea sponge *Euryspongia* sp., exhibited PTP1B inhibitory activity ( $IC_{50}$  3.6  $\mu$ M).<sup>44</sup>

### Diterpene

Liang et al investigated the PTP1B inhibitory effects of diterpenoids isolated from soft coral *Sarcophyton trocheliophorum*.<sup>183,184</sup> The diterpenoids, sarsolilide A and sarsolilide B, purified from the soft coral, exhibited in vitro PTP1B inhibitory activity.<sup>184</sup> Due to the resemblance in terms of efficiency with the hypoglycaemic agent chlorpropamide, azorellanol may act on the pancreatic  $\beta$ -cells, whereas mulinolic acid could be acting upon glucose production or utilization in the liver.<sup>185</sup>

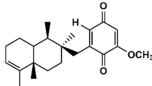
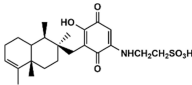
### Sesterterpene

Five sesterpenoids were isolated from marine sponge, like *Hippospongia lachne*, which is collected from Yongxin Island in the South China Sea. Among these compounds, 9-oxa-2-azabicyclo-[3,3,1]-nona-3,7-diene derivative and 2-(amino-methylene)-hepta-3,5-dienedial moiety exhibited moderate inhibition of PTP1B with  $IC_{50}$  values of 5.2  $\mu$ M and 8.7  $\mu$ M, respectively.<sup>186</sup>

### Triterpene

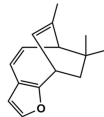
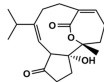
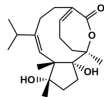
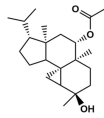
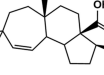
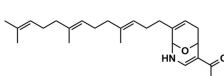
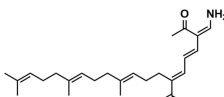
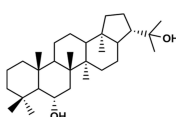
Hopane-6 $\alpha$ ,22-diol and brialmontin 1 were isolated from methanolic extract of *Lecidella carpathica*, a type of Antarctic lichen, and along with atraric acid were found to have dose-dependent PTP1B inhibitory activity with  $IC_{50}$  values of 3.7, 14.0, and 51.5  $\mu$ M, respectively.<sup>187</sup> Kinetic analysis of the inhibitory activity showed that hopane-6 $\alpha$ ,22-diol and brialmontin 1 competitively inhibited PTP1B. Compared to other protein tyrosine phosphatases such as TCPTP ( $IC_{50}$  8.4  $\mu$ M), LAR ( $IC_{50}$  >68  $\mu$ M), SHP-2 ( $IC_{50}$  >68  $\mu$ M), and protein tyrosine phosphatase receptor type C (PTPRC) ( $IC_{50}$  >68  $\mu$ M), hopane-6 $\alpha$ ,22-diol selectively inhibited PTP1B ( $IC_{50}$  3.7  $\mu$ M). Stelletin N, an isomalabaricane triterpene, was isolated from Hainan sponge *Stelletta* sp. along with other analogues, stelletin H, rhabdastrellic acid A, stelletin G, stelletin D, and 22,23-dihydrostelletin. Among the analogues, stelletin G was found to have a potent hPTP1B inhibitory activity ( $IC_{50}$  4.1 0.9  $\mu$ M). It also demonstrated a weak cytotoxicity against HL-60 and A549 cells at a concentration of 10  $\mu$ M.<sup>188</sup> In addition, isomalabaricane triterpene cytotoxicity was found to be selective towards mouse lymphoma cell line L5178Y compared to other cell lines such as HeLa (human cervix carcinoma) and PC-12 (rat pheochromocytoma).<sup>189</sup> Table 20 shows the chemical structure of the above-mentioned compounds.

**Table 20** Invertebrate-Derived Terpenes Possessing Anti-Diabetic Potential

| Species                         | Compound/Extract          | Structure  | Mechanism of Action | Reference |
|---------------------------------|---------------------------|--|---------------------|-----------|
| <i>Dysidea villosa</i> (sponge) | 21-dehydroxybolinaquinone |  | • PTP1B inhibitory  | [180]     |
|                                 | Dysidine                  |  |                     |           |

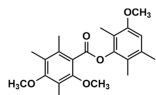
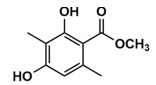
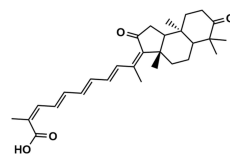
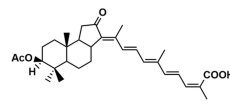
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Table 20 (Continued).

| Species   | Compound/Extract                                   | Structure  | Mechanism of Action  | Reference |
|---|--|--|--|-----------|
| <i>Euryspongia</i> sp. (sponge)                 | Dehydroeuryspongin A                               |    |  | [44]      |
| <i>Sarcophyton trocheliophorum</i> (soft coral) | Sarsolilide A                                      |    |  | [184]     |
|   | Sarsolilide B                                      |    |  |           |
| <i>Azorella compacta</i>                        | Azorellanol  |    | na   | [185]     |
|   | Mulinolic acid                                     |  |  |           |
| <i>Hippospongia lachne</i> (sponge)             | 9-oxa-2-azabicyclo-3,3,1-nona-3,7-diene derivative |  | ● PTP1B inhibitory   | [186]     |
|   | 2-(aminomethylene) hepta-3,5-dienedial             |  |  |           |
| <i>Lecidella carpathica</i> (fungi)             | Hopane-6 $\alpha$ ,22-diol                         |  | <ul style="list-style-type: none"> <li>● PTP1B inhibition</li> <li>● TCPTP inhibition</li> <li>● LAR inhibition</li> <li>● SHP-2 inhibition</li> <li>● PTPRC inhibition</li> </ul> | [187]     |

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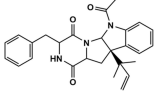
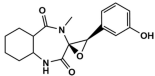
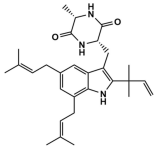
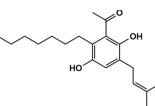
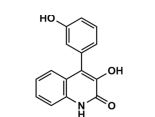
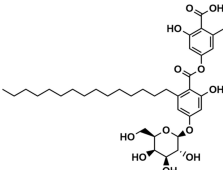
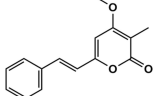
| Species                             | Compound/Extract | Structure  | Mechanism of Action  | Reference |
|-------------------------------------|------------------|--|--|-----------|
| <i>Lecidella carpathica</i> (fungi) | Brialmontin I    |  | <ul style="list-style-type: none"> <li>• PTP1B inhibition</li> <li>• TCPTP inhibition</li> <li>• LAR inhibition</li> <li>• SHP-2 inhibition</li> <li>• PTPRC inhibition</li> </ul> | [187]     |
|                                     | Atraric acid     |  |  |           |
| <i>Stelletta</i> sp. (sponge)       | Stellettin G     |  | <ul style="list-style-type: none"> <li>• PTP1B inhibitory</li> </ul>   | [188]     |
|                                     | Isomalabaricane  |  |  |           |

**Abbreviations:** TCPTP, T-cell protein tyrosine phosphatase; LAR, leukocyte antigen-related phosphatase; SHP-2, Src homology phosphatase-2; PTPRC, protein tyrosine phosphatase receptor type C.

## Others

Six different bioactive constituents, namely fructigenine A, cyclophenol, echinulin, flavoglaucin, viridicatol, and anhydrofulvic acid, isolated from marine fungal species, were found to have proven PTP1B inhibitory activity.<sup>190,191</sup> Hence, bioactive constituents isolated from marine fungus could be a potential drug target in treating diabetes.<sup>190</sup> Aquastatin A isolated from an ascomycete fungus, *Cosmophora* sp., also demonstrated a potent and selective PTP1B inhibitory activity (IC<sub>50</sub> 0.19 μM).<sup>191,192</sup> Kinetic study also showed that it inhibited PTP1B in a competitive manner. It is known to have a low IC<sub>50</sub> value against the PTP1B enzyme as well as selective PTP inhibitors such as LAR, CD45, TCPTP, and SHP-2.<sup>136</sup> The study suggested that aquastatin A exhibited such an effect due to the presence of dihydroxypentadecyl benzoic acid moiety.<sup>191</sup> Penstyrylpyrone isolated from a *Penicillium* sp. competitively inhibited PTP1B in a dose-dependent fashion. Apart from this, penstyrylpyrone was also found to inhibit NO and PGE2 via the inhibition of iNOS and cyclooxygenase-2 (COX-2) expression. Besides, through anti-inflammatory HO-1 expression, penstyrylpyrone successfully suppressed the pro-inflammatory mediator production via NF-κB pathway. Hence, by having both inhibitory and anti-inflammatory effects, penstyrylpyrone could be a potential lead agent to treat diabetes.<sup>149</sup> The marine fungi-derived anti-diabetic compounds are shown in Table 21. In addition, long-chain polyunsaturated fatty acids, namely eicosapentaenoic acid and docosahexaenoic acid, are known to exert preventive effects on obesity and metabolic syndrome. Microalgae and marine fish oil are the principal sources of these compounds. A study conducted by Mayer et al showed that the microalga, *Diacronema lutheri*, showed significant protective effect from metabolic syndrome.<sup>193</sup> Unnikrishnan et al conducted a comprehensive study involving extracts from the

**Table 21** Marine Organism-Derived Terpenes Having Anti-Diabetic Potential

| Species  | Compound/<br>Extract | Structure   | Mechanism of Action  | Reference |
|--|----------------------|---|--|-----------|
| <i>Penicillium</i> sp., <i>Eurotium</i> sp.<br>(microbe) | Fructigenine A       |    | <ul style="list-style-type: none"> <li>• PTP1B inhibitory</li> </ul>   | [190]     |
|  | Cyclophenol          |    |  |           |
| <i>Sargassum serratifolium</i><br>(macroalgae)           | Echinulin            |    |  |           |
|  | Flavoglaucin         |    |  |           |
|  | Viridicatol          |  |  |           |
| <i>Penicillium</i> sp. (microbe)                         | Penstyrylpyrone      |  | <ul style="list-style-type: none"> <li>• PTP1B inhibition</li> <li>• Pro-inflammatory mediator production via NF-κB pathway suppression</li> </ul> | [195]     |
| <i>Cosmospora</i> sp. (microbe)                          | Aquastatin A         |  | <ul style="list-style-type: none"> <li>• PTP1B inhibitory</li> </ul>   | [191]     |

edible seaweed, *Ulva reticulata*; these were investigated for their anti-diabetic effect by examining their inhibitory effects on amylase, glucosidase, and DPP-IV and antioxidant (DPPH) potential in vitro and its purified fraction using animal models. The study reported highest activity in the methanolic extract and its fraction of the seaweed.<sup>194</sup>

## Future Perspectives and Limitations

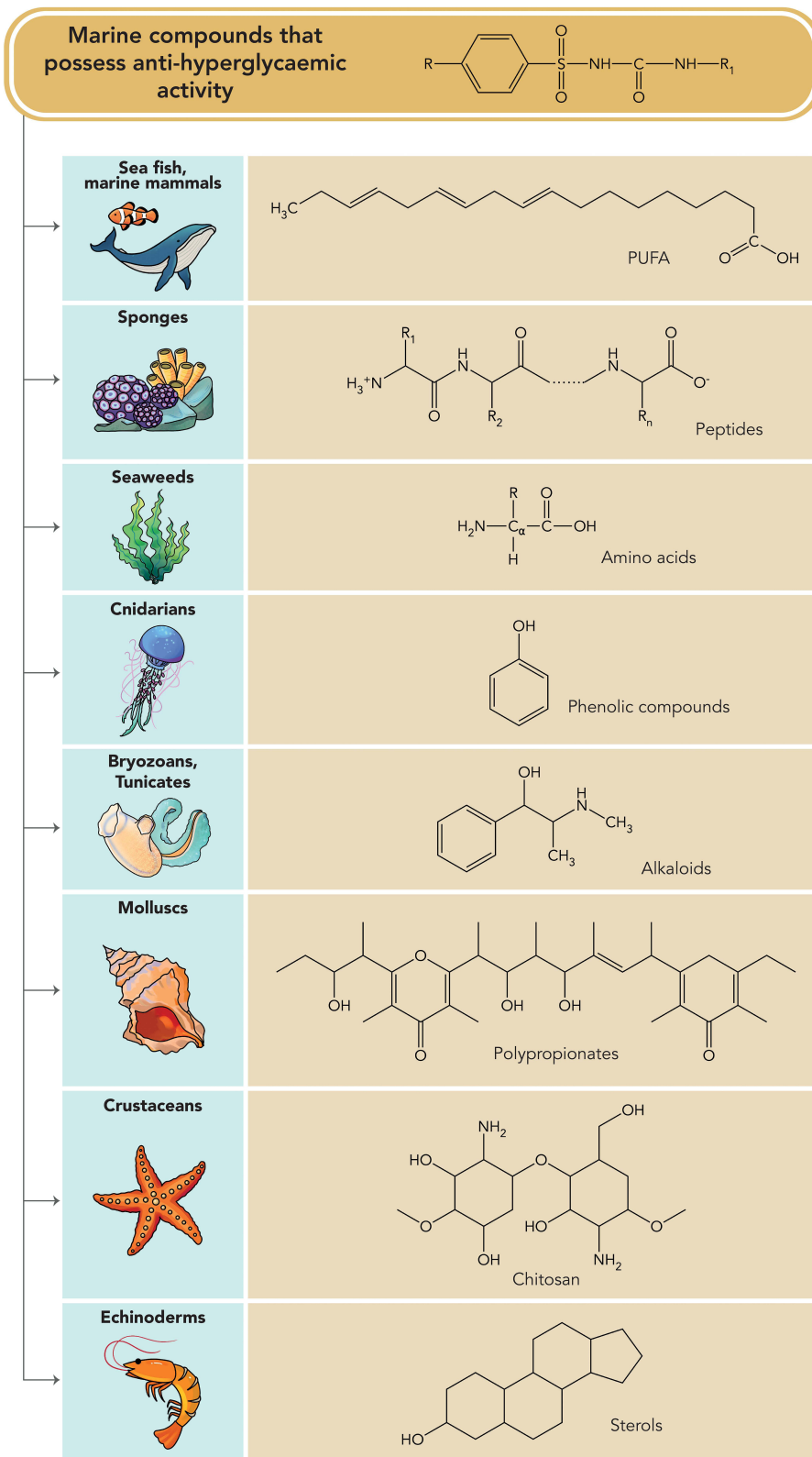
Many of the compounds and metabolites isolated from marine sources have shown potent therapeutic activities that may be used in the treatment and prevention of various ailments. However, this would only correlate to a minimal percentage of what the marine ecosystem holds. Given the enormous body of unexplored marine organisms and sources, there remains a large conglomeration of ocean life yet to be studied. Furthermore, more in-depth studies are needed for the already identified potent molecules from the marine sources. This review is an attempt to segregate the potential marine biomolecules that were reported to possess promising hypoglycaemic potential. However, unpublished knowledge may have been overlooked. Moreover, reports published outside of the search focus duration may not have been reviewed here.

## Conclusion

Due to the limited numbers of available anti-diabetic agents, marine-derived compounds (Table 22) are considered as unexploited resources of bioactive and structural compounds that have sparked significant interest among the scientific community and are anticipated to contribute to the discovery of novel hypoglycaemic agents. There is a need to pay more attention to identifying the structure–activity relationships and mechanisms of actions of these marine-derived compounds. However, limited yields of these compounds may hinder effective in vivo assessments. Hence, intensive investigations should be warranted in order to discover more effective and safer hypoglycaemic agents. Various bioactive compounds (Figure 4) isolated from marine sources compiled in this paper have exhibited hypoglycaemic effect through various mechanisms. Further studies such as toxicity tests need to be carried out in these compounds to identify the possible toxicities and identify safer hypoglycaemic agents to be used in the treatment of T2DM.

**Table 22** Anti-Diabetic Compounds Obtained from Various Marine Organisms at a Glance

| Marine Organisms      | Biologically Active Anti-Glycaemic Compounds |
|-----------------------|--|
| Sponges               | Peptide                                      |
| Marine microorganisms | Antioxidants                                 |
| Seaweeds              | Peptides, amino acids, sterols               |
| Cnidarians            | Phenolic compounds                           |
| Bryozoans             | Alkaloids                                    |
| Molluscs              | Polypropionates                              |
| Tunicates             | Peptides and alkaloids                       |
| Crustaceans           | Chitosan, minerals                           |
| Echinoderms           | Sterols                                      |



**Figure 4** Anti-hyperglycaemic compounds obtained from various marine organisms at a glance.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. The authors also took part in drafting, revising, or critically reviewing the article and have given their final approval of the version to be published. All have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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