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Potential of Seaweed in reducing Blood Glucose of Obese Type 2 Diabetes Patients

Neha Quadri*, Md. Semimul Akhtar

Shri Ram Murti Smarak College of Engineering & Technology (Pharmacy), Bareilly, Uttar Pradesh, India.

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ABSTRACT: Type 2 diabetes is a long-term disease that impairs the body's ability to process blood sugar (glucose). Insulin resistance occurs when the body either produces insufficient insulin or resists insulin. The majority of diabetes cases worldwide are Type II diabetes mellitus (T2DM), which is caused by an unhealthy diet, sedentary lifestyle, and population obesity, necessitating the search for new preventive and treatment strategies. Seaweeds contain a lot of dietary fibre, unsaturated fatty acids, and polyphenolic compounds. Seaweed bioactive components help to improve glucose tolerance while also lowering circulating lipid levels. As a result, taking seaweed supplements that are reducing the risk of type 2 diabetes complications and their composition affects type 2 diabetes.

Corresponding author*
Miss. Neha Quadri
M. Pharm Scholar
Shri Ram Murti Smarak College of Engineering & Technology (Pharmacy), Bareilly, Uttar Pradesh, India.
Tel: 91-7060589276, 8218608010
E. Mail ID: nehaquadri72@gmail.com

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INTRODUCTION:

Type 2 diabetes is a hyperglycemic metabolic disease; a condition caused either by insufficient insulin secretion or insulin resistance [1]. In most parts of the world, the number of diabetic patients is rapidly increasing. More than 34 million Americans (roughly one in ten) have diabetes, with 90 to 95 % of them having type 2 diabetes. Sedentary, obese middle-aged adults with type 2 diabetes are more likely to develop macrovascular disease, retinopathy, nephropathy, neuropathy, and hypertension [2]. These health complications result in increased morbidity and death. Specific goals of medical nutrition therapy for diabetic patients include achieving and maintaining near-normal blood glucose levels,

optimizing serum lipid levels, consuming enough calories to maintain healthy body weight, and improving overall health through a balanced intake of macro and micronutrients [3]. In general, oral hypoglycemic/antihyperglycemic agents and insulin are used to keep blood glucose levels in these patients near-normal ranges [4]. However, because these treatments are ineffective and have undesirable side effects, there is growing interest in the use of medicinal plants as an alternative treatment for type 2 diabetes. Indeed, the American Diabetes Association (ADA) recommends 20 to 35 g of total fibre per day from sources that include both soluble and insoluble fibre [5]. According to studies, eating a diet high in soluble and insoluble fiber promotes satiety, improves glycemic control, and lowers total energy intake, adiposity, and blood lipids.

Seaweeds are marine, photosynthetic algae that can be found in all oceans. In the last three decades, there has been a surge of interest in seaweeds as nutraceuticals, or functional foods that provide dietary benefits beyond their macronutrient content. Furthermore, seaweed has been mined for metabolites with biological activity in order to create therapeutic products [6]. Obesity combined with mineral and vitamin deficiency has become a health epidemic in developed regions such as Europe, the United States, and Australia. At the same time, the prevalence of dietary and lifestyle-related diseases has increased most notably type 2 diabetes, cancer, and metabolic syndrome. According to global dietary studies, countries, where seaweed is consumed on a regular basis, have significantly lower rates of obesity and diet-related illnesses. Seaweeds are commonly consumed in Asia and on occasion in the rest of the world. Non-starch polysaccharides (dietary fiber), proteins, minerals, and vitamins are abundant in edible seaweeds [7]. They are low in lipids and provide few calories. Seaweed, on the other hand, may interfere with the bioavailability of other dietary components [8]. Seaweed polysaccharides are considered a source of dietary fiber because they cannot be completely digested by human intestinal enzymes. Seaweed dietary fiber differs from land plant fiber in composition, chemical structure, physicochemical properties, and biological effects as a result; eating seaweed may increase the variety of dietary fibre [9]. There is a great deal of interest in the role of increased oxidative stress in diabetes complications. An increase in free radical production may result in increased oxidative stress. Seaweed is subjected to intense light and high oxygen concentrations, resulting in the formation of free radicals and other powerful oxidizing agents in its environment [10]. The lack of oxidative damage in their structural components (polyunsaturated fatty acids) and their stability during storage suggest that their cells have protective antioxidative systems [11]. Only a few studies on the antioxidant activity of seaweeds have been published thus far. Because seaweeds are high in polysaccharides, minerals, proteins, and vitamins, their antioxidant activity would increase their value in the human diet as well as in food and pharmaceutical supplements.

Fig 1. Sea weed for reduction of blood Glucose level obese type 2 diabetes.

Seaweed Composition and Effects on Diabetic Targets:

***Unsaturated Fatty Acids from Seaweed*:**

Unsaturated fatty acids are abundant in seaweeds. Fatty acids with two or more methylene-interrupted double bonds are important for normal cellular functions and have sparked global interest in their use as nutraceuticals, including in the treatment of T2DM [12]. The green seaweeds *U. lactuca* and *C. taxifolia* contained relatively high levels of polyunsaturated C16-fatty acids, which are uncommon in plants. C16 FAs have been proposed to be taxonomically significant in green macrophyte algae. These seaweeds also contained the essential fatty acids C18:2 (linoleic acid, n-6), C18:3 (-linolenic acid, n-3), C20:4 (arachidonic acid, n-6) and C20:5 (arachidonic acid, n-6) (eicosapentaenoic acid, n-3) [13].

***Monounsaturated Fatty Acids (MUFA) from Seaweed*:** Saturated fatty acid substitution with monounsaturated fatty acids (MUFA) was found to improve insulin sensitivity in healthy and glucose-intolerant subjects with no excess total fat intake [14]. Despite the fact that other previous studies did not find the suggested positive effects of MUFA, they are generally regarded as a useful source of fat for patients with varying degrees of insulin resistance [15]. Although the precise mechanisms of MUFA in diabetes management are still unknown, several possible modes of action have been proposed, including promoting glucose uptake by up-regulating glucose transporter type 1 (GLUT1) and type 4 (GLUT4) in the cell membrane [16], as well as having cytoprotective effects on pancreatic -cells. Furthermore, the protective effect of dietary MUFA on insulin sensitivity in rats has been attributed to the preservation of the IRS/PI3K insulin pathway and increased GLUT4 translocation to the cell membrane. MUFA has also been linked to changes in incretin responses and gastric emptying, with dietary MUFA raising glucagon-like peptide (GLP-1) levels in both healthy and diabetic subjects [17]. Furthermore, dietary MUFA consumption increased adiponectin levels, which are linked to a lower risk of T2DM. Wang and colleagues discovered that extracts and MUFA derivatives isolated from the green seaweed Ulvalactuca induced many ARE-driven antioxidant genes in a variety of mouse tissues [18]. As discussed in the following section, one of the anti-diabetic properties of seaweed has been reported to be antioxidant, anti-inflammatory properties, and stimulation of hepatic antioxidant enzymes [19].

***Polyunsaturated Fatty Acids (PUFA) from Seaweed*:** Polyunsaturated fatty acids (PUFA), like MUFA, play a variety of important biological functions in nature, both structural and physiological [20]. They also play a role in cellular and tissue metabolism, such as thermal adaptation and membrane fluidity regulation [21]. Furthermore, rising public interest in a healthy lifestyle and diet has propelled PUFA into popular market demand. Seaweed's potential as a good source of PUFA has been well documented [22]. Seaweed may contain lipids, which can account for up to 2 % of algal dry weight and are primarily PUFA. The majority of the PUFA found in seaweed are omega-3 and omega-6 fatty acids, both of which are essential in the human diet and are found in almost equal amounts. *Undaria pinnatifida*, *Himanthalia elongata*, and *Laminaria ochroleuca* contain a higher percentage of unsaturated fatty acids (MUFA and PUFA) than saturated fatty acids, with *U. pinnatifida* containing nearly 70 % of fatty acids as PUFA [23]. A balanced diet should include omega-3 and omega-6 fatty acids in an appropriate ratio, with an ideal ratio of 1:3 to 1:5 of omega-3 to omega-6 fatty acids, as this affects the ratio of resultant eicosanoids [24].

***Dietary fibers from Seaweed*:**
Dietary fiber consumption has been linked to weight loss due to a slower gastric clearance rate, which leads to increased satiety and a reduction in food intake. Previous large-scale prospective observational studies have shown that high dietary fiber intakes are consistently associated with a significantly lower incidence of T2DM [25]. Many international organizations have issued guidelines recommending high daily dietary fiber intakes ranging from at least 30 g/day for healthy individuals to 50 g/day for diabetic patients. Many seaweed species have comparable or higher total fiber content than their terrestrial counterparts [26]. *Himanthalia elongata*, *Ascophyllum nodosum*, *Laminaria digitata*, and *Palmaria palmata*, for example, have a higher percentage of total dietary fibre and a lower percentage of soluble carbohydrate (g/100 g weight) than brown rice and bananas. Reduced glucose and blood lipid levels, as well as increased antioxidant enzyme activity, are among the benefits [27].

Epidemiological Evidence and Dietary Intervention Studies:

In the Western world, the prevalence of chronic dietary-related disorders such as type 2 diabetes, obesity, and cardiovascular disease has reached epidemic proportions. Pharmaceutical drugs are frequently used as first-line therapy by the medical profession to treat disorders and their symptoms. While these can be beneficial, many conventional drugs have serious side effects and lose efficacy over time. The nutritional intervention has long been proposed as a solution for both preventing and treating chronic dietary-related health problems. However, when compared to data from pharmaceutical studies, where effective doses are specified at the micro-molar level, this is frequently regarded as anecdotal evidence [28]. In recent years, the fields of natural products chemistry and pharmacognosy have advanced, elucidating numerous plants, fungal, and algal compounds with therapeutic properties. Because of their mineral-rich marine habitat and the requirements to

survive in this environment, seaweed has chemical properties that are distinct from terrestrial plants [29]. To combat abiotic stress such as UV photo-damage, high salinity, constant oxygen exposure, and biotic stress from bacterial colonization and marine herbivores, seaweeds produce antioxidising, antimicrobial, and other bioactive agents. Various seaweeds, either as part of the diet or as isolated extracts, have been shown to have disease-preventive properties. The epidemiological evidence from large population studies and controlled experimental interventions demonstrating the beneficial effect of seaweed in the diet on a variety of human health disorders is discussed.

Type 2 diabetes:

In 1980, there were 108 million adults worldwide who had diabetes (4.7 % of global population) and (8.5 % of the global population). Type 2 diabetes accounted for 90 to 95 % of these diabetic cases. About 7.7 % of adults in the United Kingdom are currently diagnosed with type 2 diabetes. In the United States, it is 9.1 %, with an additional 86 million (26.4 % of the population) suffering from pre-diabetes [30]. Type 2 diabetes mellitus, also known as adult-onset diabetes, is a diet-related metabolic disorder that responds well to dietary intervention, as opposed to type 1 diabetes (an autoimmune disorder) that destroys the beta cells of the pancreas and requires insulin injections to be treated. Acarbose, a -amylase and -glucosidase inhibitor, is commonly used to treat type 2 diabetes and may cause gastric discomfort and diarrhea. Many animal studies have shown that seaweed has anti-diabetic properties in vivo. In human clinical trials, daily supplementation with Undaria pinnatifida and Sacchariza polyschides (as Gigantea bulbosa) balances blood glucose levels, lowers serum triglyceride concentrations, and raises high-density lipoprotein cholesterol in type 2 diabetes patients [31]. Another study looked at how a commercial seaweed extract (InSea2) affected postprandial plasma glucose and insulin concentrations. The InSea2 extract contained natural -amylase and -glucosidase inhibitors as well as Fucus vesiculosus and Ascophyllum nodosum. *In vitro*, the extract demonstrated anti-diabetic properties by inhibiting these digestive enzymes that convert polysaccharides into simple sugars in the intestine and raise blood glucose levels. Twelve subjects were given capsules containing 500 mg InSea2 powder 30 min before a meal of 50 g white bread, while a control group received placebo capsules Plasma glucose levels were reduced by 9 % in the seaweed group for 3 hours after meal consumption (1188 mmol L–1 min–1 in the placebo group compared to only 1081 mmol L–1 min–1 in the seaweed group), though the difference was not statistically significant (P >.05) [32]. The seaweed group, on the other hand, had a significant insulin reduction of 12.1 % in plasma levels. Furthermore, peripheral insulin sensitivity and muscular glucose uptake (Cederholm index) improved by 7.9 %. The improvements in glucose and insulin profiles caused by seaweed extracts suggest that they could be used to maintain insulin homeostasis in type 2 diabetes patients. Seaweed's anti-diabetic action has been attributed to compounds such as phlorotannins, fucoxanthin, polyphenolics, and polysaccharides**.**Which inhibits hepatic gluconeogenesis and decreases the activity of digestive enzymes like -amylase, -glucosidase, lipase, and aldose reductase. Seaweeds and their extracts may help to alleviate the type 2 diabetes health epidemics, which can cause nephropathy, blindness, peripheral neuropathy with limb extremity loss, and premature death [33].

Hypertension and cardiac disease:

Hypertension raises the risk of cardiovascular disease more than other factors such as smoking and type 2 diabetes. Non-modifiable risk factors such as age, gender, ethnicity, and genetics play a role in the aetiology of hypertension and cardiovascular disease; however, modifiable risk factors such as diet and lifestyle can be improved to significantly reduce the risk of developing high blood pressure and heart disease Numerous pharmaceuticals for the treatment of high blood pressure and heart disease, such as the angiotensin-converting enzyme (ACE) inhibitor Captopril and the aldosterone inhibitor Eplerenone, have been developed. They are effective, but they can cause side effects such as persistent dry cough, impaired kidney function, and extremely low blood pressure [34]. Lipitor and other statins lower LDL cholesterol to combat hyperlipidaemia and slow the progression of atherosclerosis. Statins, on the other hand, can cause muscle myopathy, elevated blood sugar, impaired liver function, and memory loss. Epidemiological studies have found an inverse relationship between regular seaweed consumption and a lower risk of hypertension and cardiovascular disease [35]. A 15-year study of dietary patterns in 79,594 Japanese men and women (aged 45 to 75) discovered that adherence to Japanese dietary guidelines was associated with a lower risk of

death from all causes and cardiovascular disease, particularly cerebrovascular disease, within the experimental population. In Japan, 3.3 g day1 of U. pinnatifida powder was used in a dietary intervention trial on 36 elderly outpatients with hypertension. A placebo was given to a control group of 18 gender-matched subjects (age 2 years). After 4 weeks, the seaweed group's systolic blood pressure dropped by 13 mmHg, and by 8 mmHg after 8 weeks [36]. After 4 weeks, diastolic pressure dropped by 9 mmHg, and by 8 mmHg after 8 weeks. Furthermore, hypercholesterolemia in the treatment group decreased by 8 % after 4 weeks. Studied *U. pinnatifida* in a similar manner. Powder (6 g per day) was given to 30 men and women with metabolic syndrome for one month. When compared to the placebo group, all participants in the seaweed group had a significant decrease in systolic blood pressure (10.5 mmHg) and a reduction in waist circumference (3.6 cm, in women only) [37]. In human cell culture and animal in vivo trials, peptide extracts of seaweeds can significantly lower blood pressure in single doses and long-term administration. Peptides have the ability to bind to the active site of the angiotensin-I converting enzyme, lowering blood pressure. Peptides extracted from Gracilariopsis lemaneiformis, for example, had potent ACE-inhibitory activity *in vitro*. Sulphated polysaccharides from Ulva prolifera (as Enteromorpha) reduce hyperlipidaemia in animal models, which is one of the primary causes of heart disease [38]. Seaweed's eicosapentaenoic and docosahexaenoic acids may also play a role in the mechanism of heart disease risk reduction [39]. These n-3 fatty acids can have an antiarrhythmic effect in cardiac cell membrane phospholipids by influencing ionic channels and maintaining intracellular calcium homeostasis [40].

Cancer:

Seaweeds are classified as food by the US Food and Drug Administration, European Pharmacopoeia, and European Food Safety Authority, not as medicine [41]. However, in many Asian countries, seaweeds are considered medicinal and are packaged with information about their effects and how to use them [42]. Japanese and Korean pharmacopoeias, as well as the Chinese Marine Materia Medica, contain examples. Because seaweed has been used as a regular part of the diet and accepted as medicine in Asia for millennia, it is possible that the majority of epidemiological evidence originating there is due to this. 39 food groups were used to assess risk factors for the development of biliary tract cancer [43]. Only four food groups had a significantly positive or negative association with biliary tract cancer risk factors. Seaweed, allium (onions and garlic), salted meats, and preserved vegetables were among these categories (pickled with salt-brine). Both the seaweed and allium groups had an inverse relationship (i.e. lower risk) with cancer [44].

The salted meat and preserved vegetable groups were linked to a lower risk of cancer (increased risk). The authors hypothesised that seaweed's high fibre and anti-inflammatory properties reduced this group's risk of developing cancer. A case-control study of breast cancer in South Korea found that consuming several species of Pyropia (as Porphyra) on a daily basis was inversely related to the risk of developing cancer. Pyropia (known as 'gim' in Korea) is commonly consumed dried and roasted [45]. A group of 362 women with histologically confirmed breast cancer (aged 30 to 65) and 362 control participants of similar age and menopausal status completed a food frequency questionnaire containing 121 food items, including seaweed, over a 12-month period [46]. An inverse dose-response association with the risk of breast cancer was seen in women who consumed the most gim over the twelve months (at least 1.17 g/day, dry mass) [47]. The multiple mechanisms by which seaweeds induce apoptosis in cancer cells have been linked to several compounds such as fucoxanthin, polyphenols and other antioxidants; phlorotannins; iodine; and sulphated polysaccharides such as fucoidan [48].

Obesity and metabolic disorder:

According to the Organization for Economic Cooperation and Development, 38.2 % of the adult population in the United States was obese in 2015, compared to only 3.7 % in Japan and 5.3 % in Korea [49]. Obesity, when combined with mineral and vitamin deficiency, has become a public health crisis in many developed countries [50]. Obesity raises the risk of other diseases such as type 2 diabetes, hypertension, dyslipidaemia, and coronary heart disease [51]. Consumption of fibre-rich foods such as seaweed and seaweed isolates containing carotenoids and alginate has been linked to improved appetite, satiety, blood glucose, and cholesterol levels. Seaweed and its extracts could be used to treat obesity in conjunction with lifestyle changes such as exercise and dietary changes [52].

Antibacterial properties:

Despite the development of antibiotics in the 1940s, the global burden of infectious diseases caused by bacteria, viruses, fungi, and protozoans continues to rise [53]. The issue in the Western world is not the availability of antimicrobial treatments, but the development of microorganism immunity to pharmaceutical drugs and disinfectants. Bacteria, in particular, pose a risk because of their ability to evolve and survive within human hosts and on surfaces [54]. Drug-resistant bacterial infections such as *Pseudomonas aeruginosa*, *Helicobacter pylori*, *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and methicillin-resistant Staphylococcus aureus kill at least 700,000 people worldwide each year (MRSA). Drug-resistant bacteria are expected to kill 10 million people per year by 2050, outnumbering cancer. In the fight against antibiotic-resistant infectious bacteria, seaweed products provide alternatives to conventional antibiotics. Several compounds found naturally in seaweed have antibacterial efficacy comparable to pharmaceutical drugs [55].

Antioxidants:

Free radical damage to living cells, such as reactive oxygen species, has been linked to a variety of chronic diseases. Although humans' endogenous defense mechanisms can combat free radical oxidation to some extent, many people still have an imbalance, especially if their diet is low in antioxidants and they are under a lot of stress. Epidemiological studies have found that dietary compounds like phlorotannins and fucoxanthin can lower the risk of developing disorders like metabolic syndrome, cancer, cardiovascular disease, osteoporosis, renal disease, Parkinson's, Alzheimer's, and neurodegenerative disorders [56].

Anti-Diabetic Properties of Seaweed:

Fucoxanthin, alginate, and other compounds found in seaweed help lower blood sugar levels, lowering the risk of diabetes. The review of seaweed's anti-diabetic potential is generally not homogeneous because certain seaweed components, bioactive compounds, and mechanisms of action have been studied more extensively than others. Aside from unsaturated fatty acids and dietary fibres, research on anti-diabetic properties involving polyphenols from seaweed is much more prevalent, with a variety of polyphenolic compounds isolated against many well-known anti-diabetic targets. Polyphenolic compounds have been shown to form complexes with numerous proteins, and those derived from vegetables and fruits have a variety of activities, including anti-diabetes [57].

Reduction of Glucose Levels via Inhibition of α-Glucosidase and α-Amylase Activities:

Starch digestion in mammals is primarily accomplished by -amylase and -glucosidase in the small intestine, and abrupt postprandial elevations in blood glucose concentrations are caused by carbohydrate hydrolysis [58]. Maltose and isomaltose produced by -amylase action are then hydrolyzed by -glucosidase, a membrane-bound enzyme found in the small intestine epithelium, yielding glucose [59]. Inhibiting both -amylase and -glucosidase activities can significantly reduce the post-prandial rise in blood glucose after a mixed carbohydrate intake and is a logical approach in managing glucose levels in borderline and T2DM patients. Several seaweed extracts and bioactive compounds were found to significantly inhibit the activities of these carbohydrate hydrolytic enzymes [60].

Bioactive Seaweed Compounds against Diabetic Targets:

Marine seaweeds have recently been discovered to be a rich source of bioactive secondary metabolites that may have human health benefits [61]. Fucoxanthin is the most abundant accessory pigment found in brown seaweeds and has been linked to powerful biological activities such as anticancer, antioxidant, and anti-diabetic properties due to the presence of an unusual allenic bond and a 5, 6-monoepoxide in its structure.

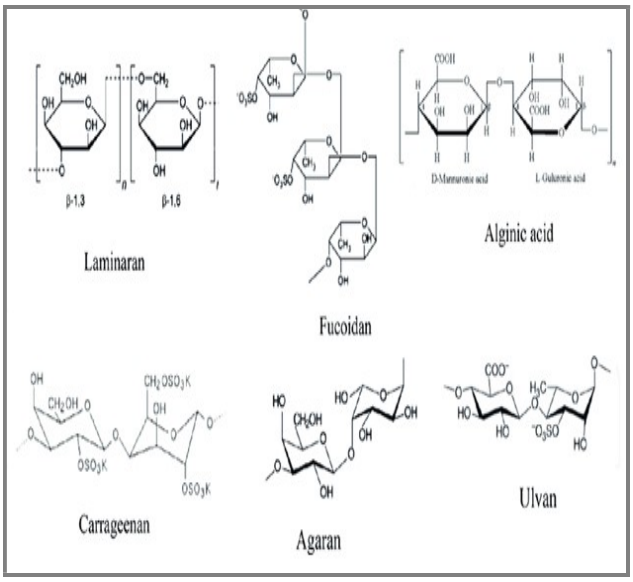

Fig 2. Chemical structures of sulfated polysaccharides present in marine sea weed.

Green seaweed has a protein content ranging from 10 to 26 %, according to studies. Red seaweeds with the highest protein content, such as *Phorphyra tenure* and *Palmaria palmata*, had a protein content of around 47 % [62].

There are numerous compounds isolated from various seaweed species that inhibit - glucosidase activity. Dieckol is one example, as previously stated. The inhibitory activity of BDDE (IC50 = 0.03 M) from *S. latiuscula* is greater than that of BDDE (IC50 = 0.098 M) from *O. corymbifer* and *P. lancifolia*. Similarly, eckol (IC50 = 11.16 M) isolated from E. maxima was more potent than the same compound isolated from *E. stolonifera.* Dioxinodehydroeckol and 7-phloroeckol are two other notable examples. Indeed, the carbolytic enzyme inhibitory activities of fucoidan isolated from *Ascophyllum nodosum* and *Fucus vesiculosus* varied according to season and species. Fucoidan, a water-soluble polysaccharide, inhibited the activities of -glucosidase and -amylase differently depending on the collection period and target enzyme Fucoidan extracted from *A. nodosum* inhibited both -glucosidase and -amylase, whereas fucoidan extracted from *F. vesiculosus* inhibited only -glucosidase. Fucoidan from *A. nodosum* also reduced -amylase activity by 7 to 100 % at 5 mg/ml, with IC50 values ranging from 0.12 to 4.64 mg/ml depending on the seaweed collection period [61-64].

CONCLUSION:

In this review, we will discuss the contents and diverse bioactive compounds isolated from seaweed. Type 2 diabetes is a hyperglycemic metabolic disease caused by either insufficient insulin secretion or insulin resistance, both of which have been shown to be potentially beneficial in T2DM management. Indeed, seaweeds, particularly edible species, contain a wide range of compounds with diverse modes of action involving both specific mechanisms such as interaction with critical proteins and broad non-specific mechanisms such as anti-inflammatory response and antioxidant enzyme up-regulation. All of these can be useful in T2DM treatment strategies. Polysaccharides and dietary fibres found in seaweed may improve postprandial satiety, resulting in lower blood glucose levels and improved insulin sensitivity. Seaweed dietary fibres are also beneficial in reducing body weight or maintaining weight, and thus in lowering the risk of obesity. Phenolic and non-phenolic compounds isolated from seaweed have beneficial effects on T2DM hallmarks such as hyperglycemia and hyperlipidaemia. Therefore, seaweed and seaweed-derived bioactive compounds possess huge potential to be employed in T2DM management either as part of dietary intake or as purified pharmacological agents and supplements.

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