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Seaweeds as a potential resource in diabetes management: a review

J. S. Vidyashree[1], Priya P. Shetti[2*] and Shridhar C. Ghagane[2]

Abstract

Background Seaweeds are the marine macroalgae predominantly found in the coastal regions. These species have unique chemical profiles which makes them stand different from terrestrial plants. They are found to be rich in secondary metabolites which have potential in treating various unhealthy conditions. Diabetes is a chronic condition where an individual suffers from high or low sugar levels in the blood.

Main text This review article aims to review such seaweed species that are potent in treating and managing diabetes. It has become one of the rapidly growing diseases in the world with a high occurrence rate. This paper details the mechanism of glucose regulation in the human body. Seventy percent of the total earth's surface is accomplished by marine ecosystem. It offers home for about 25,000 species. Among them, many possess health benefits hence these are utilized directly as food or in the form of medicine.

Conclusion In this article, various such seaweed species which have antidiabetic property has been discussed. Including edible seaweeds in daily diet have numerous healing properties. Inhibition of alpha amylase and alpha glycosidase enzyme has been associated with lowering the postprandial glucose level. This review article attempts in exploring how seaweeds and managing diabetes are interrelated.

Keywords Seaweed, Macro algae, Diabetes, Alpha amylase, Alpha glycosidase, Antidiabetic

Background

Diabetes mellitus, commonly referred to as diabetes, is categorized as a group of metabolic diseases that arise when either the pancreas is unable to produce sufficient insulin to support the body's normal blood sugar mechanism or when the body is unable to efficiently utilize the insulin that is already produced. Pancreas has two main functions, out of which one is endocrine function that regulates blood sugar. β-islets of Langerhans cells in the pancreas produce insulin, a peptide hormone whose purpose is to maintain a normal blood glucose level. It is achieved by regulating carbohydrate, lipid, and protein metabolism, facilitating cellular glucose uptake. Insulin is encoded by INS gene. Hyperglycemia refers to elevated levels of glucose in the blood. This condition is commonly associated with diabetes, a chronic disease that affects the body's ability to regulate blood sugar. The lack of insulin's action on the target tissue or its secretion in pancreatic cells is the primary reason for increased glucose ±levels in blood [1]. One more condition is low blood sugar called hypoglycemia. Diabetes comprises of two major types, Type 1, in which the pancreas produces little or no insulin over time, is a chronic condition. Type 2 diabetes is characterized by elevated blood glucose levels because of either absolute or relative insulin deficiency. The decrease in beta-cell mass or impairment in beta-cell function is the cause of this drop-in insulin levels or insufficient insulin secretion [2]. About 90% of

*Correspondence:
Priya P. Shetti
priyaguddad77@gmail.com
[1] Dr. Prabhakar Kore Basic Science Research Centre, Department of Biotechnology, Jawaharlal Nehru Medical College, Belagavi, Karnataka 590010, India
[2] Dr. Prabhakar Kore Basic Science Research Centre, KLE Academy of Higher Education and Research, Nehru Nagara, Belagavi, Karnataka 590010, India

cases of diabetes are type 2 [3]. It is primarily the result of an unhealthy lifestyle, excess weight, and lack of physical activity. Initially, only adults were more prone to type 2 diabetes, now it is affecting among children as well.

Incidence and mortality rate

Diabetes has had the fastest incidence rate over a decade. Its prevalence has increased from 108 million in 1980 to 422 million in 2014. In 2015, the count rose to 451 million among the individuals aged between 18–99 [4]. In 2017, type 1 diabetes affected 9 million people; the majority of the cases were reported from high-income countries. By 2021, only children and adolescents (ages 0 to 19) will make up more than 1.2 million. Neither its cause nor the means to prevent is known. Polyuria, that is excessive urination, polydipsia (increased thirst), persistent hunger (polyphagia), weight loss, blurry vision, and fatigue are some of the symptoms in this instance.

Diabetes as a global health issue

According to the recent publication by IDF diabetes organization published in 2021, worldwide, approximately 537 million adults suffer from diabetes, and the number is expected to rise to 643 million by 2030 and 783 million by 2045. China currently has the highest number of adults aged 20 to 79 with diabetes, followed by India and Pakistan. Every 3 in 4 adults are living with diabetes now. About 240 million adults with diabetes are undiagnosed and has resulted in 6.7 million fatalities. Twenty-one million pregnant women are at risk of getting affected by diabetes during their pregnancy [4]. It is medically termed as gestational diabetes. They have the risk of developing type 2 diabetes later at any point of time of life. T2DM affects 541 million adults at an increased risk. The reason it is being categorized as global health issue is due its increased risk of effecting other parts of the organ system. Increase in blood sugar levels might risk the patient in leading way to other diseases, such as glaucoma, cataract, blindness, chronic kidney disease, neuropathy, hypertension, and other heart diseases.

Prevalence

Global diabetes prevalence is estimated to be 9.3% in 2019, or 463 million people. By 2030, it will rise to 10.2% (578 million) and by 2045, to 10.9% (700 million). Urban areas have a commonness rate of 10.8%, while rural areas have a commonness rate of 7.2%. In low-income nations, the prevalence rate is 4%, while it is 10.4% in high-income nations [5]. Half of the population—one in two, or 50.1%—is unaware that they have diabetes. In 2019, the global prevalence of impaired glucose tolerance is estimated to be 7.5 percent (340 million), rising to 8.6 percent (548 million) in 2030 and 2045 [5]. Obesity especially central obesity and increased visceral fat due to insufficient physical activity along with the consumption of high calorie diet, high sugar-based diets are the contributing factors.

Treatment

Till today, there is no exact medication or complete cure discovered for diabetes. Diabetes can be treated by monitoring the sugar levels, switching to healthy lifestyle, practising physical activities that could be yoga, cycling, running any activity of people's choice. Most of the treatment for type 1 diabetes involves injecting exogenous insulin and by oral medications to sustain normal healthy life [6]. Regular screening from physicians in case of any complications is mandatory requirement. Modifications in lifestyle will be a selfcare treatment which includes proper and healthy diabetic diet, exercising regularly, weight management, nutritional counselling, keeping count on carbohydrate intake. For type 2 diabetes, metformin is typically prescribed [7]. It actions primarily by making the liver produce less glucose and enhancing the body's sensitive to insulin, allowing it to use insulin way more effectively.

Management

Most people manage their diabetes themselves. No matter how advanced the treatment technology is, the outcome will be poor if the patient is unwilling or unable to manage it on a daily basis [8]. Management of diabetes includes following a proper healthy diet, physical exercise, and keeping their daily sugar and carb intake in control. Regular physician visits and check-ups also help. Now, technology has evolved so much, and we have many diabetes testing kits through which we can monitor blood glucose level just in fraction of time at home. The American Dietetic Association introduced medical nutrition therapy (MNT) in 1994 to better explain the nutrition therapy process for diabetic patients. This program explains how to use specific nutrition services to treat a condition, injury, or illness. MNT for diabetes consists of a four-step procedure that, when followed correctly, can help reduce the risk of developing diabetes. They are.

i. Assessing the patient's diabetes self-management abilities and nutrition knowledge.

ii. These are designed and tailored for each person, identifying, and negotiating nutritional goals.

iii. Nutritional intervention that combines the patient's needs with a flexible approach to meal planning and education materials so that the patient can put the plan into action.

iv. Keeping tabs on all the activities and evaluating the outcomes.

These are essential for patients to acquire and maintain the knowledge, skills, mindset, behaviour, and commitment necessary to successfully face daily diabetes self-management challenges [9].

Indulging oneself in physical activity is another one such process which is known to have numerous health benefits, both general and specific to diabetes [10]. Practising yoga is found to be an effective way in managing diabetes. Lifestyle related modifications, ditching sedimentary living style and participating in any active form can make an individual lessen the risk of developing diabetes. People with obesity are much prone to diabetes. Weight management is an added advantage. Despite significant advances in diagnosis and treatment, the persistence of inadequate metabolic control continues. Patients fail to manage diabetes on their own and even clinicians' ineffective approaches to intervention which may contribute to poor glycaemia control [11].

Glucose enters our body through food. Absorption of this food, the breakdown of glycogen and gluconeogenesis are the three main ways where body cells meet the glucose. Glucose is stored in the form of glycogen in liver and the biochemical pathway of generating glucose from non-carbohydrate substrate in the body is called gluconeogenesis. Insulin plays a significant role in balancing glucose levels in body [12]. The pictorial representation of mechanism of glucose regulation in humans is explained in Fig. 1.

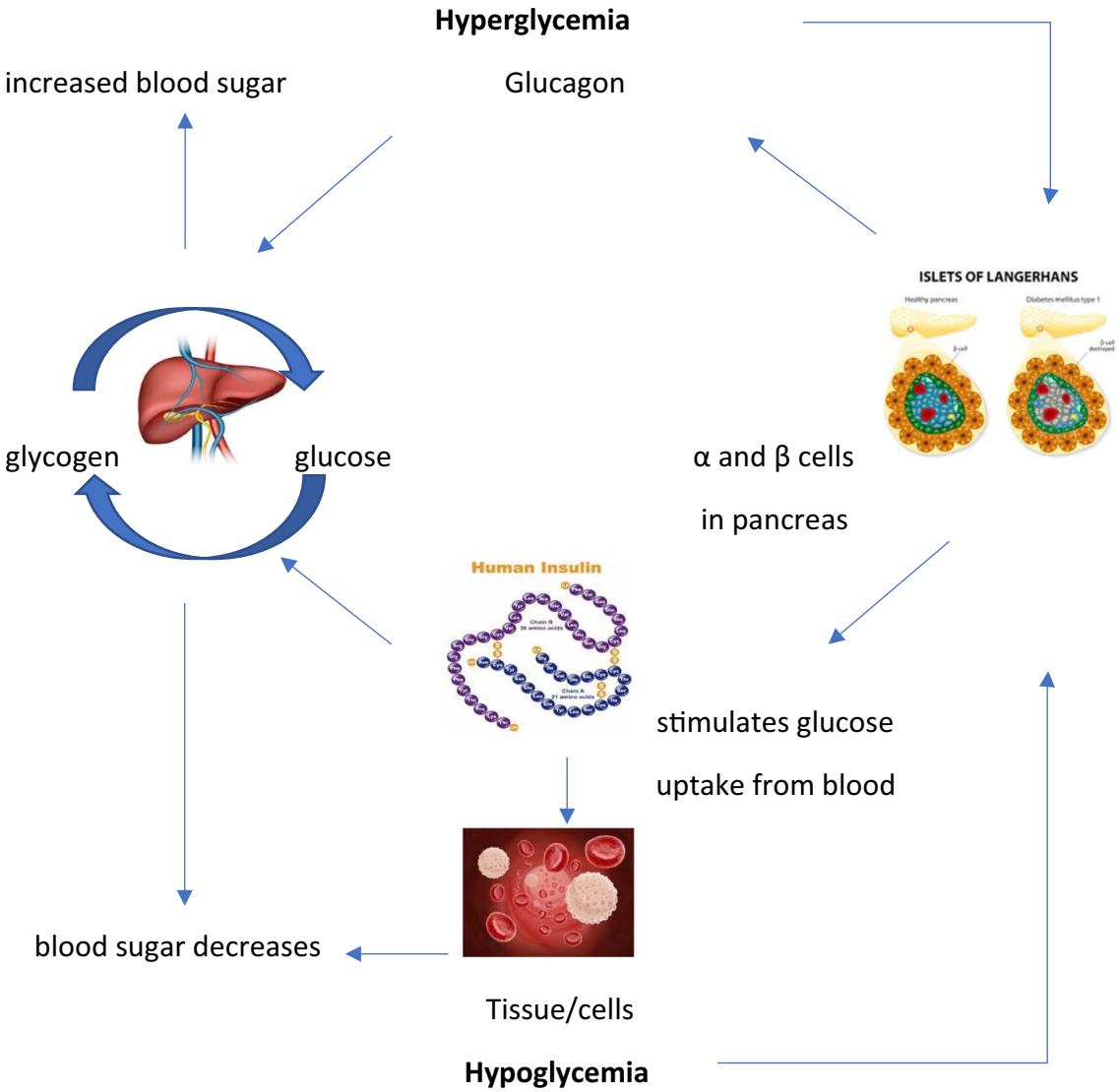

Fig. 1 Mechanism of glucose regulation

Main text

Seaweeds

Seaweeds are naturally occurring marine macroalgal species which are found in marine environment. These are adapted to salt conditions provided by seas and oceans. During monsoons, these seaweeds are carried to the seashore along with the waves due to the increase intensity of waves. They are usually found attached to the rocky substrate or any other solid surface along the seaside [13]. They are macroscopic, multicellular, and completely different form of higher plants. Seaweeds do not possess true or definite roots, stem, or leaves [14]. Seaweeds are highly pigmented, based on their pigmentation, they are put into three main algal classification, Rhodophytes (red algae), Phaeophytes (brown algae), and Chlorophytes (green algae).

Brown algae constitute of 16 orders with approximately 285 genera and 1800 species. They are the largest and fastest growing of all the seaweeds. They exhibit a rich composition of pigments of different biosynthetic origins. Chlorophyll *a* and *c,* carotenes particularly α-carotene and β-carotene and xanthophylls. They also exhibit fucoxanthin, violaxanthin and diatoxanthin. Red seaweed is second largest phyla of algae containing over seven thousand species currently recognized. Chlorophyll *a,* phycocyanin, phycoerythrin and phycobilin are the pigments that give red colour to these species. Chloroplasts in green algae contain chlorophyll a and b, which gives them their bright green colour. They are also rich in carotene (red orange) and xanthophylls (yellow) in their stacked thylakoids (Fig. 2).

Marine macroalgae are the promising source for bioactive secondary metabolites which has vast application in drug developments, pharmaceutics and other biotechnological applications [15]. There is an increasing demand for macroalgae and macroalgae derived food. Bioactive compounds are the chemical constituents that are present in the species which has an influence on a living organism, tissue or a cell. They have the capability of regulating or deregulating on specific disease or damage caused to the cell when used in correct manner. They are often referred to as secondary metabolites [16]. This property of theirs is demonstrated by conducting basic research which could be in-vivo (inside the organism's body) or in-vitro (in controlled environment outside the organism's body). Seaweed species are found to have potential phytochemical constituents which are capable of being antioxidant, anti-inflammatory, anticancer, antidiabetic agents. Hence, they play a key role in pharmaceutical industry. These are also used in cosmetics.

Seaweeds and diabetes

Much research works on seaweeds have found out the presence of phytochemical constituents that are responsible in treating and managing diabetes. Including edible seaweeds in daily diet and its regular consumption is associated with the reducing the risk of developing diabetes. A variety of polyphenolic compounds have been isolated from seaweed which are well known for their target against diabetes [17]. According to the studies, some of the seaweeds may be able to prevent enzymes from hydrolyzing carbohydrates in-vitro and lowering effect of blood glucose was noticed in-vivo after the consumption of meal [18]. Bioactive compounds derived from seaweed play a significant role in glucose-induced oxidative stress and the reserve of starch-digestive enzymes [19]. In diabetic patients, the levels of antioxidant parameters tend to decrease, so in this such case, many studies have proven that phytochemicals that can exert antioxidant and free radical scavenging activities can improve the body's sensitivity to insulin.

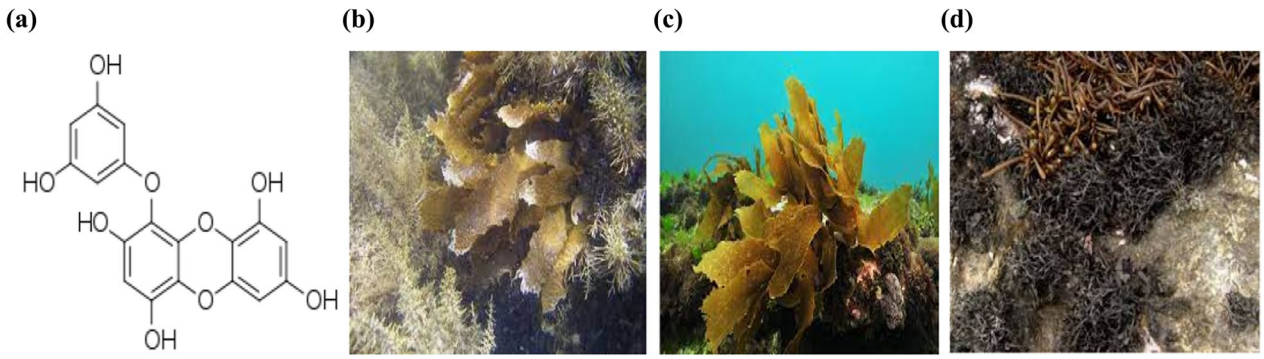

Fig. 2 **a** Structure of phlorotannin, **b** *Ecklonia stolonifera* rich in eckol, **c** *Ecklonia cava* rich in dieckol, **d** *Ishige okamurae* rich in diphlorethohydroxycarmalol

Phaeophytes

Phaeophytes possess number of active constituents like phlorotannins which is a unique secondary metabolite, that has got specified biological activities [20]. Studies on brown seaweeds have suggested that these species influence in glycemic management and could be benefit patients with type 2 diabetes. Fucales, dictyotales and laminariales are the majorly used orders of phaeophyceae that are extensively used for the extraction of secondary metabolites [21]. Species belonging to fucaceae are great with phytochemicals that have great interest from industrial point of view. Phlorotannins, a class of marine-only polyphenols, have received a lot of attention in recent years due to their enormous potential for therapeutic use [22]. Brown algal species contain significant number of phenolic compounds, a polysaccharide which has got extensive high biological activities. These phytochemicals are found to be more effective as antioxidants when compared to green and red algal species [23].

Phlorotannins are class of phenolic secondary metabolites which has a wide range of biological treatments. Research on this has proven phlorotannins to have antidiabetic, antioxidant, cancer, inflammation, adipogenesis, and numerous other biomedical uses [24]. They are synthesized by polyketide pathway (acetate-malonate pathway) produced by the polymerization of phloroglucinols [25]. These can be later extracted from various extraction methods such as chromatography [26]. α-amylase and α-glucosidase are the two digestive enzymes that are responsible for digestion of carbohydrates and increase the postprandial glucose level in diabetic patients. By inhibiting the enzymatic action of these two enzymes, postprandial hyperglycemia, and the risk of developing diabetes can be reduced.

Brown seaweeds are also rich in fucosterol and its derivatives [27]. This compound was first isolated from *Cystoseia foeniculaceae* and *Dictyota ciliolate* by RP-HPLC method. A fraction of the compound was analysed by NMR technique [28]. Polyphenols found in some species of brown algae support the algae's structural development and protect them from biotic and abiotic stress conditions [29, 30]. It has been reported that marine brown algal species with sulphated polysaccharides possess useful therapeutic properties. Fucoidan has antioxidant and antidiabetic potential. Fucoxanthin is an accessory pigment of some of the algal species. *Fucus*, *Dictyota* and *Laminaria* are rich in carotenoids and even used for extracting it from them. This active constituent has proved to exhibit antioxidant, anticancer and antidiabetic activities [31].

Red seaweeds

Red seaweeds are major source of vitamins, minerals, calcium and magnesium. They are widely consumed as food in many continents. Bromophenols from red algae have been reported for antidiabetic activities. They are the source of dietary fibres promoting health benefits like lowering bad cholesterol and regulate blood sugar levels. Rhodophytes are rich in sulphated polysaccharides [32]. These SPs were associated in combating different oxidative stress induced diseases [33]. Experiments on red and green seaweeds have proven that they possess inhibiting properties of α-glucosidase enzyme [34]. *Rhodomela confervoides* (Fig. 3a), *Symphyocladia latiuscula* (Fig. 3b) and *Polysiphonia urceolata* (Fig. 3c) consists of bromophenols, 2-piperidione, benzene acetamide, n-hexadecanoic acid and polysaccharide derivatives that were found to exhibit hypoglycaemic potential by inhibiting α-glucosidase [34]. Red seaweeds are beautiful home for hydrocolloids specially, agar and carrageenans. Hydrocollloids are extracted from them and are widely used in diverse medicinal and food industries [35].

Fig. 3 **a** *Rhodomela confervoides*, **b** *Symphyocladia latiuscula*, **c** *Polysiphonia urceolata*

Polysaccharides have significant antidiabetic effects in multiple ways, most notably by preventing gastric emptying, inhibiting the activities of amylase and glucosidase, increasing insulin secretion, and improving insulin function [36]. As a result, polysaccharides derived from algae may be effective treatments for diabetes and its complications.

Green seaweeds

Green seaweeds belong to the genus Ulva, they have been reported to possess hypoglycemic activity. Due to their high soluble fibre content, they are used for various food dishes in Asian countries. The aqueous extract of green seaweeds *Ulva lactuca* (Fig. 4a) (Inhibition-α-amylase: 83.4%; α-glucosidase: 61.81%) and *Ulva reticulate* (Fig. 4b) (Inhibition-α-amylase: 89.1%; α-glucosidase: 76.02%)were effective against the enzymes α-amylase and α-glucosidase at a concentration of 100 g/ml after an 8-h extraction period at 37 °C in a water bath, allowing the phytochemicals and colloids to be released into the extract more slowly. Similarly, the crude extract of *Ulva ohnoi* (Fig. 4c) exhibited α-amylase inhibition by 41.7% and complete α-glucosidase inhibition at 10 mg/mL [15, 37, 38].

Reducing postprandial hyperglycemia is one of the healing methods in diabetes management. This can be achieved by reducing carbohydrate hydrolyzing enzymes in the digestive tract suspending glucose absorption. The breakdown of carbohydrates is mostly done by α-amylase and α-glucosidase. Delay in the release of glucose from dietary multiple carbohydrates sources results in the decreased postprandial plasma glucose and hyperglycaemia level [39]. By simultaneously absorbing glucose from the intestine and breaking down starch with pancreatic α-amylase, α-glucosidase and -amylase react to digest in the human body. By hydrolyzing inner 1,4-glycosidic linkages, pancreatic amylase determines the degree of starch digestion and produces linear and branched malto-oligosaccharides. These are then acted upon by α-glucosidase enzymes, which play a crucial role in the conversion of carbohydrates into glucose and may initiate postprandial hyperglycaemia [40].

Alpha-glucosidase is responsible for the ultimate step of hydrolysis of starch or disaccharides into simple glucose units, while alpha-amylase is involved in the digestion of long-chain carbohydrates. As a result, inhibitors of these enzymes delay the absorption of glucose, lowering the blood glucose level after eating [41]. A protease enzyme called dipeptide peptidase-IV participates in the breakdown of incretins, which are a group of metabolic hormones that cause the ß cells of the Langerhans islet to release insulin. Incretins are delivered after supplement admission, and they postponed gastric discharging and decline glucagon emission notwithstanding feeling of insulin discharge [42].

Alpha-amylase participates in the digestion of long-chain carbohydrates, while alpha-glucosidase is responsible for the final step in the hydrolysis of starch or disaccharides into simple glucose units. Therefore, inhibitors of these enzymes delay the absorption of glucose, resulting in a drop in blood glucose levels following a meal [1]. Incretins, a class of metabolic hormones that trigger insulin release from the ß cells of the Langerhans islet, are broken down by a protease enzyme called dipeptide peptidase-IV. After taking a supplement, incretins are given. Despite the sensation of insulin being released, they delay gastric emptying and reduce glucagon release [43].

Marine macroalgae are found to have bioactive compounds which have DPPH-IV inhibiting potential. Dipeptidyl peptidase IV is also referred to as adenosine deaminase complexing protein 2 which is an enzyme present in human body [44]. It is a protein encoded by DPP-IV gene. This enzyme destroys incretin. Incretins are the group of hormones that stimulates a decrease in blood glucose levels [45]. Its main physiological role in human body is to regulate the amount of insulin that is secreted after the consumption of food. DPPH-IV inhibitors block

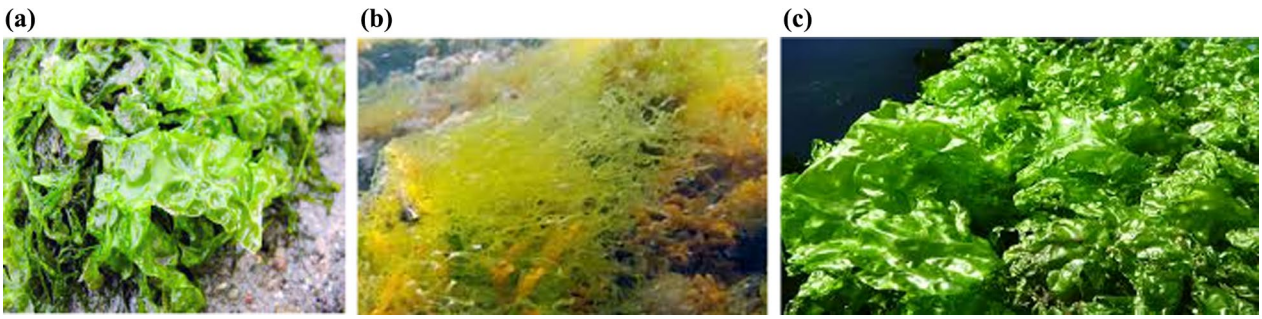

Fig. 4 **a** *Ulva lactuca*, **b** *Ulva reticulate*, **c** *Ulva ohnoi*

the action of this enzyme, which destroys this hormone incretin. This hormone is responsible to produce insulin only when there is a need of it. Therefore, reducing the amount of glucose being produced by liver [46] (Table 1).

Seaweeds in food and nutrition

Seaweeds which are fit for human consumption are put under edible seaweed lists which are widely been consumed by Asian countries. Chinese consume seaweeds as traditional medicine. Koreans use seaweeds as a key ingredient in their soups. Women consume seaweed soup after childbirth which is known to boost their immunity and strengthen them along with infant's health. When consumed in the appropriate amounts, edible seaweeds are known to offer a rich and long-lasting source of macronutrients and micronutrients for human consumption [47]. *Porphyra tenera* and *Palmaria palmata* are the red seaweeds which contain elevated levels of proteins that is 47.5 and 30%, respectively [48]. Nori or purple laver, the edible seaweeds belonging to *Porphyra* species, a blackish-purple seaweed that enhances the flavour of sushi, which is a Japanese ethnic food usually wrapped with rice. It is mostly grown in China, Japan, and the Republic of Korea [49]. Nori is the most widely produced product from marine culture in Japan. Some of the edible seaweeds with their regional names are mentioned in Table 2.

In the recent article, possibilities of using seaweed capsules which function as a needle-free life for diabetic patients was published on The Economic Times, Tokyo. It further stated that researchers have created a novel capsule using seaweed extract to preserve insulin-producing pancreatic cells, giving diabetics hope for an injection-free treatment. Insulin injections are administered daily to patients with type 1 diabetes [50]. Pancreatic islet transplantation is a successful treatment that can eventually reduce or eliminate insulin dependence completely. Cryopreservation is the general method of preserving and transporting the cells [51]. This process also comes with a disadvantage of sharp ice crystals that can break and pierce into cell membrane and compromise with cell viability.

Although seaweeds being highly nutritious and carry benefits when consumed in proper manner, they are attached with some minor limitations. Marine species though available in huge mass, they are time and temperature restricted. Distinct species need different environmental condition for their active and optimum growth [52]. Their unavailability throughout the year becomes a limitation. As these are marine species, they need intense cleaning and specific storage conditions. Seaweeds possess elevated levels of iodine which when consumed might lead to high levels of iodine in some people which might lead conditions like hyperthyroidism.

Table 1 Different seaweed species with their antidiabetic potential

Seaweed	Class	Bioactive compound used	Nature of study	Refs.
Sargassum kjellmanianum	Brown	Polysaccharide-alginate	In-vivo In-vitro	[42]
Ecklonia cava	Brown	Phlorotannin-Dieckol	In-vivo	[1]
Cystoseira compressa	Brown	phlorotannin	In-vivo	[43]
Laurencia dendroidea	Red	Bromophenols	α-glucosidase α-amylase	[44]
Sargassum confusum	Brown	oligosaccharides	In-vivo	[45]
Sargassum horneri	Brown	fucoidan	In-vivo	[46]
Macrocystis pyrifera	Brown	polysaccharide	In-vivo	[47]
Pelvetia siliquosa	Brown	Fucosterol	–	[48]
Grateloupia elliptica	Red	2,4,6-Tribromo phenol	α-Glucosidase inhibition	[49]
Polysiphonia morrowii	Red	3-Bromo-4,5-dihydroxy benzyl alcohol	α-Glucosidase inhibition	[50]
Gelidium amansii	Red	β-D-galactopyranose and 1,4-linked 3,6-anhydro-α-L-galactopyranose units	In-vivo	[51]
Gracilaria opuntia	Red	sulphated galactopyran	α-amylase and α-glucosidase inhibition	[32]
Hypnea spinella	Red	sulfated polysaccharide	In-vivo	[36]
Enteromorpha prolifera	Green	–	Inhibition of the JNK1/2 insulin pathway in liver of mice	[52]
Chaetomorpha aerea,	Green	–	Inhibition against alpha-amylase	[45]
Chlorodesmis	Green	z,z-6,2 8-heptatriactontadien-2-one	α-amylase inhibition	[45]

Table 2 Edible seaweeds consumed in different part of the world with their regional names

Seaweed	Image	Common name
Ascophyllum nodosum		Egg wrack
Laminaria digitate		Kombu or konbu
Laminaria saccharina		Sweet kombu
Himanthalia elongate		Sea spaghetti
Undaria pinnatifida		Wakame
Porphyra umbilicalis *Porphyra vietnamensis*		Nori
Palmaria palmata		Dulse or Dillisk
Chondrus crispus		Irish moss
Ulva lactuca		Sea lettuce

Conclusion

Seaweeds offer 60% of marine species in the world. They have unique chemical profile which makes them withstand high salinity conditions. They are usually categorized as unwanted plants in the coastal regions. But these plants are macroalgae which possess various health benefits for humans when consumed as part of their daily diet. Seaweeds have all the potential to the overcome the diseases, such as diabetes, cancer, inflammation. They are distinct from terrestrial species due to the presence of distinct bioactive compounds in them. Diabetes is a disease where a person's body either does not produce enough insulin required for normal metabolism or body's inability to accept the insulin. The cause for the diabetes is numerous. As it is one of the lifestyle related disorder, making changes in the living style and switching to a healthy and organized lifestyle can help overcome it. Seaweeds serve enough macronutrients and micronutrients and other essential dietary fibres which when consumed in daily diet can reduce the risk of developing such lifestyle related disorders like diabetes, cancer, etc. Hence, studying these seaweeds species is equally important. In this review article, various research papers on treating diabetes with different seaweed species were studied. Alpha amylase and alpha glucosidase are two digestive enzymes which are responsible for digestion of sugars in the gut itself in postprandial cases. Many of the seaweeds have the potential to inhibit these enzymes which helps in curing diabetes. These studies revealed that, the seaweeds can be used as food, has significant role in medicine, pharmaceuticals, beauty and other industries. So, this study concludes that, such healthy species should be identified and can be used in treating diabetes. This article lays background to the seaweed research area giving an overview for the research scholars sharing equal interest in the area.

Abbreviations

MNT	Medical nutrition therapy
NMR	Nuclear magnetic resonance
RP-HPLC	Reverse phase high performance liquid chromatography
DPPH	2,2-Diphenyl-1-picrylhdrazyl

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Author contributions
VJ has done data collection and major contributor in review manuscript writing. PS has designed the concept, corrections, and SG has done drafting of the manuscript. All the authors have read and approved the manuscript. The authors are thankful to Dr. Prabhakar Kore Basic Science Research Centre, Department of Biotechnology, Belagavi, 5900010, Karnataka, India.

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