Review

Antioxidant and Antidiabetic Activity of Algae

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Abstract: Currently, algae arouse a growing interest in the pharmaceutical and cosmetic area due to the fact that they have a great diversity of bioactive compounds with the potential for pharmacological, cosmetic, and nutraceutical applications. Many of these bioactive compounds are secondary metabolites whose amounts in the algae vary with varying environmental conditions. Free radicals and other active oxygen derivatives are recognized as a natural by-product of aerobic metabolism. However, reactive oxygen species directly participate in mechanisms related to various pathological states such as cancer, diabetes, atherosclerosis, Alzheimer's, and Parkinson's, among others. Diabetes mellitus (DM) is a metabolic disease resulting from changes in glucose metabolism and/or deficient production/action of insulin. This review has as its main objective to reveal the potential antioxidant and antidiabetic capacity of algae extracts.

Keywords: diabetes; antioxidant; antihyperglycemic; lipid profile; body weight; algal treatments

1. Introduction

The prevalence of diabetes has increased rapidly over the past few years, mainly in low to middle-income countries, and has become one of the major causes of premature death worldwide. According to International Diabetes Federation (IDF) [1], there were about 537 × 10^6 individuals living with diabetes, and about 316 × 10^6 persons suffer from weakened glucose tolerance and augment risk of diabetes. These statistics are predictable to increase to 643 × 10^6 by 2030, and it prophesied less than a quarter of a century, there will be 783 × 10^6 people suffering from this disease without rapid and accurate prevention procedures [1].

Diabetes mellitus (DM) is an extended metabolic disorder of several etiologies characterized by chronic hyperglycemia with the ailment of carbohydrate, fat, and also protein metabolism, which is usually due to an absolute or relative lack of insulin, impaired effectiveness of insulin action or tissue insensitivity to insulin [2].

Insulin is a hormone produced by the pancreatic β-cells that functions to maintain strict control of blood glucose. This hormone makes it possible for the tissues and cells of the body to use glucose for energy. If the insulin is absent or its action is impaired due to tissue insensitivity, cells and tissues are unable to uptake glucose, causing its accumulation in the blood. Consequently, symptoms of diabetes occur [3].

Symptoms of diabetes often go unobserved because they can be attributed to many other reasons and some patients fail to notice cautioning signs or practice definite indicative symptoms [4]. However, possible symptoms diabetes may include the following: Unexplained weight loss, excessive thirst (polydipsia), excessive urination (polyuria) and dehydration, excessive hunger and general fatigue, blurred vision, nearsightedness or other vision problem, and vaginal infection. The control of hyperglycemia (abnormally

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high glucose) is very important in the treatment of all forms of diabetes because, in the long term, acute and chronic complications can happen when the blood glucose concentration is not kept in the normal range [2].

There are various categories of diabetes: type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational *Diabetes mellitus* and other specific categories of diabetes that are caused by several reasons, such as pancreatic or drug-related diseases, monogenic diabetic syndrome and chemical inducers [5]. The two main types of diabetes mellitus were illustrated in Figure 1. Type 1 diabetes is also identified as insulin dependent *Diabetes mellitus* (IDDM). It represents about 10% of all cases of diabetes. Previously known as juvenile-onset diabetes and usually occurs in persons under 40 years of age [6,7]. In this type, there is usually a lack of the secretion of insulin as a result of disorders affecting and deteriorating the pancreatic β-cells ,and it is conveyed to have a genetic preparedness and an autoimmune basis that lead to β-cell destruction due to the presence of insulin antibodies [5]. Patients need a daily dosage of insulin to live and avoid the progress of ketoacidosis. As a result of insulin insufficiency, the body will be forced to burn fats instead of glucose for energy, resulting in a toxic byproduct called ketones under severe hyperglycemia [8].

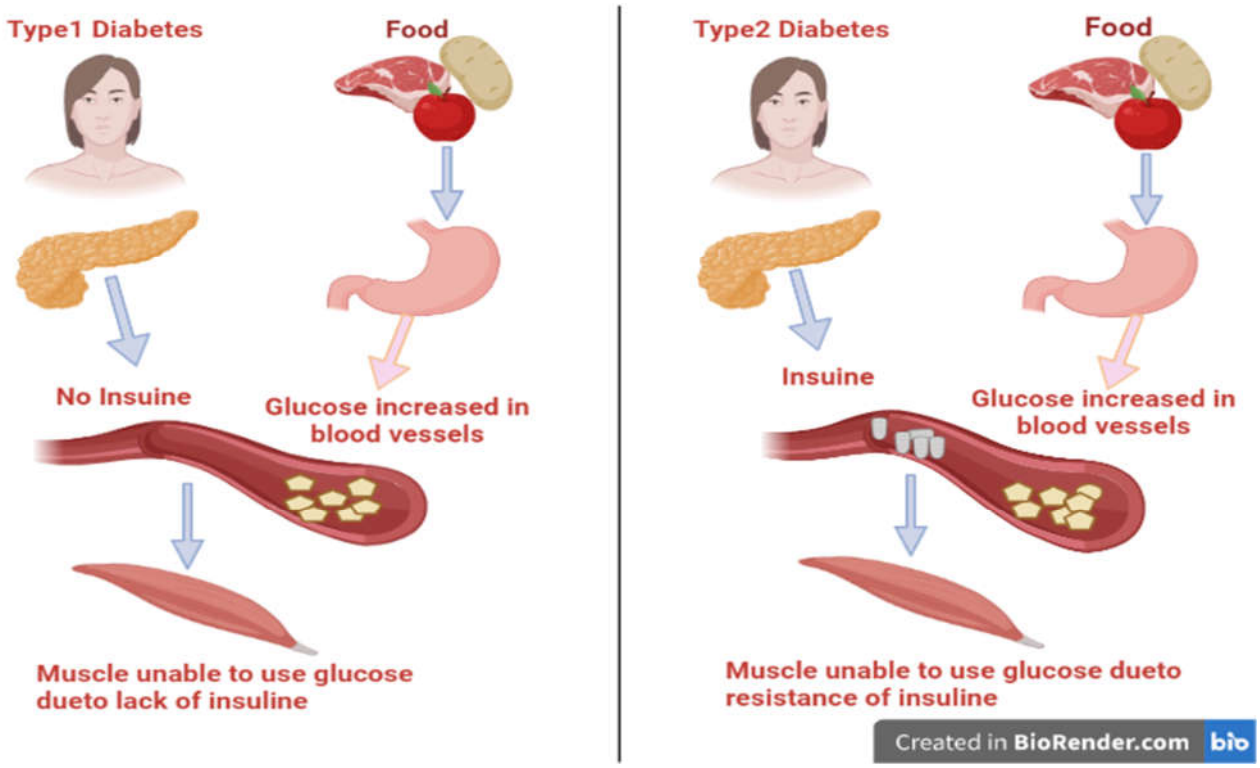

Figure 1. Types of *Diabetes mellitus* and their syndrome.

Alternatively, Type 2 affects about 95% of people diagnosed with *Diabetes mellitus* and people that are 40 years and above [9]. It occurs as a result of the progressive loss of β-cells secreting insulin or tissue insensitivity to absorb insulin leading to impaired insulin action [10]. Thus, the aim of this review is to comprehensive review of how algae can be useful in the diabetes therapeutics and prevention. Thus, an important step due to the globalization of fast food and fast food-based diseases.

2. Factors contribute to diabetes and its complications

Majority of this disease types, all over the world, may be correlated to modern diet, sedentary lifestyle and obesity. The mortality associated with diabetes is mainly as a result of the augmented danger of several complications of this disease. Even though diabetes is primarily defined by chronic hyperglycemia, many diabetic patients, particularly those

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with type 2, have elevated blood pressure (hypertension), chronic high levels of insulin (hyperinsulinemia), and abnormal levels of cholesterol, triglycerides, and/or other blood lipids (hyperlipidemia). In addition, lipoprotein abnormalities are some of the most prevalent problems associated with type 2 diabetes (T2DM)[11]. These complications are closely linked to the disease disorders and strictly linked to its diagnoses and treatment procedures (Figure 2).

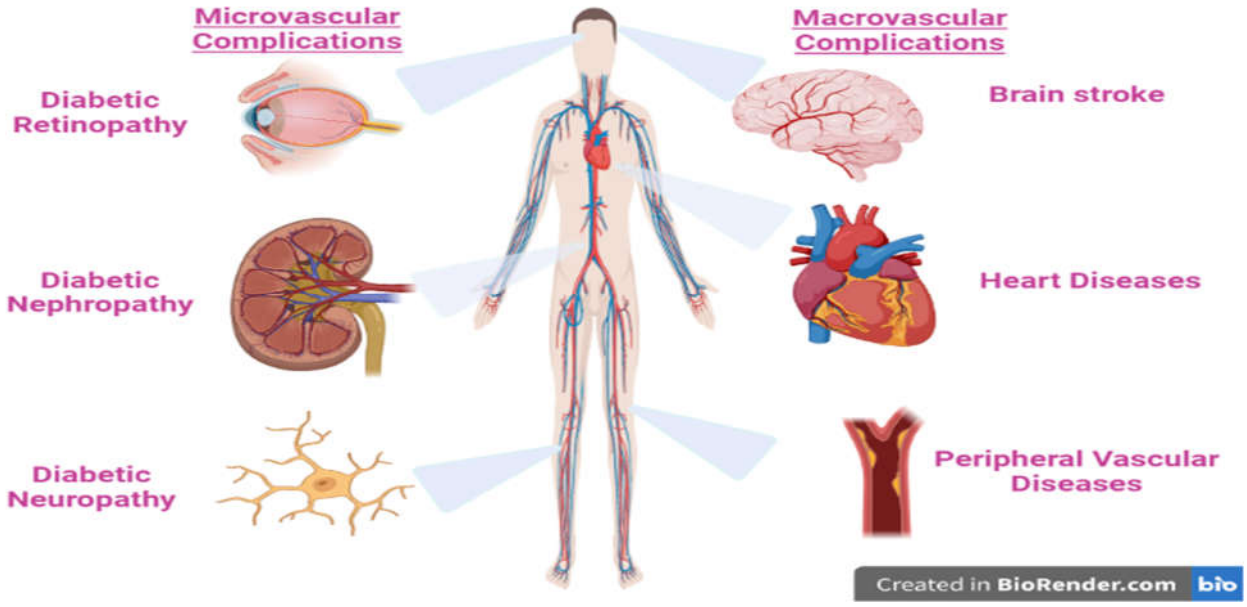

Figure 2. The major complication of type 2 *Diabetes mellitus*.

2.1. Oxidative stress linked to diabetes

Biochemical processes in the body may produce harmful intermediate products called reactive oxygen species (ROS). These free radicals have one or more unpaired electrons that make them very reactive with other molecules. Excess ROS may lead to an imbalance in its production and in the body's ability to detoxify or counteract the harmful oxidant effects of these free radicals [12,13]. This condition is known as oxidative stress, the degree of which depends on the balance between ROS production and antioxidant defenses [14]. Oxidative stress is thus the result of imponderables between the formation and neutralization of reactive oxygen and nitrogen species [15,16]. Electron transfers to O_2 is catalyzed by oxidases to produce chemical energy or oxidation of substrates. These enzymes are potential sources of partially reduced Cu^{2+} derivatives in biological settings; they also produce $O_2^{\bullet-}$ during catalysis [17-19]. The mitochondrial electron transport chain reduces O_2 to $O_2^{\bullet-}$ [20,21], which was reduced by dismutase to form hydrogen peroxide (H_2O_2) and/or further reacted to form the hydroxyl secondary radical ($^{\bullet-}OH$) or reactive oxygen species (ROS) [17,19]. Although the cause-effect relationship remains unsure, there appears to be a strong correlation between mitochondrial dysfunction and chronic metabolic diseases such as obesity [17] and Diabetes mellitus (Figure 3) [22]. This, in turn, results in oxidative damage of cellular components in the form of lipid peroxidation, protein denaturation or DNA conjugation, and, finally, cell death [23]. Because of the aforementioned reasons, oxidative stress has been related to many diseases like cancer, post-

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ischemic and neural degradation, Parkinson's and Alzheimer disease, AIDS (acquired immune deficiency syndrome), aging and cardiovascular diseases [24].

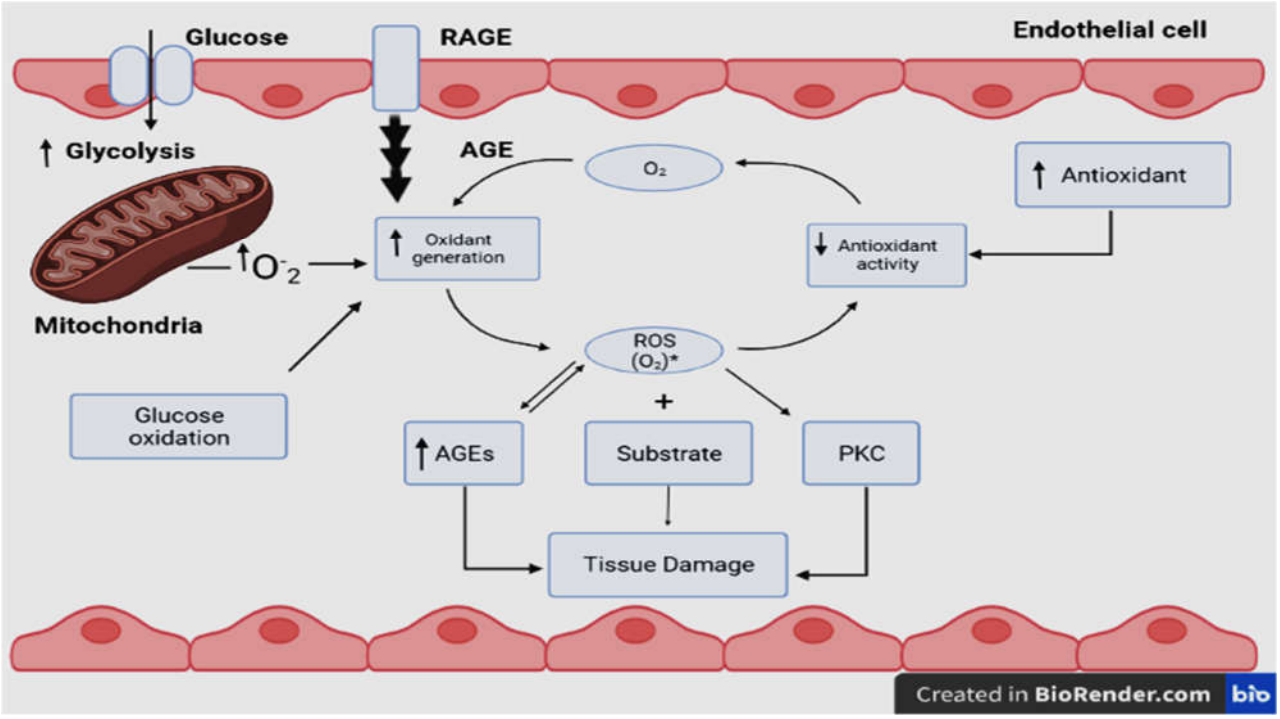

Figure 3. Relationship between rates of oxidant generation, antioxidant activity, oxidative stress, and oxidative damage in Diabetes.

3. Treatment of Diabetes

Diabetes requires changes for a lifetime. Diabetes necessitates lifelong adaptations. One key objective of the cure is to offer the diabetic patient with the tools needed to achieve the best possible management of glycemia, blood pressure, and lipidemia in order to avoid, postpone, or stop the microvascular and macrovascular consequences of diabetes [25]. Currently, the available medicine for treating type 2 diabetes works by stimulating and augmenting endogenous insulin production at target tissues, as well as blocking common diabetic enzymes such as - amylase and -glucosidase enzymes [26]. Enzymes such as α-amylase and α-glucosidase act synergistically in the human body through the breakdown of starch by pancreatic α-amylase and the absorption of glucose by intestinal α-glucosidase [27,28]. α-amylase is the main enzyme that regulates the digestion rate of starch by the hydrolysis of inner linkages α-1,4-glucosidic, and forming linear and branched malt-oligosaccharides. These are then acted on by α-glucosidases, which perform a role in the conversion of carbohydrates into glucose, and this may lead to postprandial hyperglycemia. Reducing postprandial (after-meal) hyperglycemia levels has been well-thought-out one of the furthermost functional therapeutic processes by inhibition of pancreatic α-amylase and α-glucosidase, which delays the carbohydrate digestion and glucose absorption significantly with scarcer drawbacks than earlier diabetic treatments [7,29,30].

Some synthetic inhibitors of these enzymes used clinically to manage or remedy diabetes such as sulfonylureas, biguanide, glycosidase inhibitors, insulin, aldose reductase inhibitor, thiazolidinediones, carbamoyl methyl benzoic acid gliclazide, metformin, acarbose and voglibose have been practiced [31]. Continuous use of this synthetic agents, should be limited because they may be the reason of flatulence, abdominal cramps, vomiting, diarrhea, weight gain, nausea, upset stomach and liver function disorders [32,33].

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Increased efforts are being made to find and investigate potential inhibitors of α-glucosidase and α-amylase from natural sources to develop compounds for use in antidiabetic medications *in vitro* and *in vivo* showing no side effects [34].

3.1. Antioxidants

Antioxidants are constituents that delay or avoid the oxidation process by neutralizing or the free radicals scavenging in body cells [35].

The main source of antioxidants for the body is vegetables and fruits [36,37]. There are countless commercial synthetic antioxidants for example butylated hydroxyl toluene (BHT), propyl gallate (PG), butylated hydroxy anisole (BHA) and tert-butylhydroquinone (TBHQ), which are used to reduce the harmful effects of free radicals. But these synthetic one may cause other side harmful effects [38]. The search to replace these artificial antioxidants with novel resources of natural antioxidants has become a critical exploit in immune pharmacy discovery meanwhile their use in food products has been failing off due to their instability or their suspected action as promoters of carcinogenesis [39].

Natural antioxidants from natural origin can react rapidly with these free radicals and retard or alleviate the extent of oxidative deterioration [40]. Furthermore, antioxidants from natural sources can help in the increasing of the foods shelf life. Therefore, the consumption of antioxidant materials could protect the body and the foods against these actions [41]. In recent times, studies suggest that there is a contrary relationship between dietary intake of antioxidant rich foods and the incidence of human disease. These materials presumed to have several positive health effects which include prevention of cardiovascular disorders and certain types of cancer and may possibly decrease the mutations potential [42].

Moreover, they may be a dynamic, safe, and economical substitute cure for diabetes managing and organs protection [43]. Natural antioxidants include tocopherols, ascorbic acid, carotenoids, flavonoids and related polyphenols, α-lipoic acid, glutathione, phlorotannins, alkaloids and flavonoids [44]. Fortunately, majority of these compounds are natural components of plants and algae as secondary metabolites.

3.2. Algae and their bioactive components linked to diabetes treatment

The expression of algae represents a great group of diverse organisms from dissimilar phylogenetic groups and also, representing several taxonomical divisions. Generally, algae may be mentioned as plant-like organisms that are regularly photosynthetic and aquatic, but without real roots, stems, leaves, vascular tissue and have elementary reproductive structures. They are distributed worldwide in the seawater, freshwater and wastewater [45]. They have two major types according to their forms and sizes.

They can be as single microscopic cells and as macroscopic multicellular organisms or live in colonies (microalgae). Cyanobacteria, previously known as blue-green algae, are morphologically various divisions of prokaryotic, photosynthetic organisms that flourish in varied types of habitats. Most species of blue-green algae are free-living in freshwater, marine, or terrestrial, and symbionts in accompanied by other plants and lichens [46].

They can grow in a leafy shape, as in the case of seaweeds (macroalgae) such as giant kelp. Picoplankton is between 0.2 to 2 μm in diameter, while the fronds of giant kelps are as large as 60 m in length. Lastly, algae are found in a range of aquatic habitats, both freshwater, and saltwater [47]. The term seaweed refers to the large visible macroalgae growing and attaching to rock and along the seashore. Seaweeds have been used widely for multipurpose applications such as human food, animal feeds, and fertilizers [48].

Seaweeds are primitive plants which grow extensively in shallow marine water and estuaries. Generally, seaweeds are scientifically classified as Rhodophyta (red algae), Phaeophyceae (brown algae) and Chlorophyta (green algae). These classifications are determined due to their pigments, nutrient, chemical composition, morphological and anatomical characteristics [49].

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The natural products derived from algae such as alkaloids, flavonoids, terpenoids, steroids, and phenols have received considerable attention over the years due to their diverse pharmacological properties and they might be acted synergistically to pursue antioxidant and antidiabetic functions [50]. From these compounds alkaloids which have cytotoxic activity inhibiting the formation of the mitotic spindle fibers required for cell division [51]. Terpenoids display a wide spectrum of antitumor activities [52]. Steroids are recognized to have antimicrobial and cardiotonic properties and play a vital role in nutrition, herbal medicine, and cosmetics [53]. Tannins were used therapeutically as antiviral, antibacterial, antiulcer and antioxidant agents as well as inflammation as cytotoxic [54].

Flavonoids, phenolic compound, have antimicrobial, antioxidant or free radical scavengers and spasmolytic activity [55]. Other biological compounds like saponins are used in hypercholesterolemia, hyperglycemia, antioxidant, anticancer, anti-inflammatory and weight loss drugs [56]. Among the bioactive components which were noticed in the different algal extracts, and they have been found in photosynthetic microalgae also [57,58] and proved to exert antioxidant activities are the phenolic compounds. These are a large chemical group that have been associated with defense mechanism against endogenous and exogenous effects, such as oxidative process, light, temperature and pathogens invasion [59].

3.3. Antioxidant and antihyperglycemic activity of algae

The therapeutic potential of microalgae may be linked to its biological compounds such as alkaloids, carotenoids, terpenoids, steroids, phlorotannins, phenolic compounds, halogenated ketones, alkanes and cyclic polysulfides, in addition to being rich in proteins, vitamins, pigments, lipids and essential minerals [60]. In agreement, butanol extract from *Arthrospira platensis* (formerly *Spirulina platensis*) (Cyanobacteria) (Figure 4a) showed the maximum antioxidant activities with DPPH (2,2-diphenyl-1-picrylhydrazyl), reducing power, hydroxyl radical and nitric oxide scavenging activity [61]. In the same manner, Jayshree et al. [62] investigated that *Chlorella vulgaris* (Chlorophyta) (Figure 4b) methanolic extract showed antioxidant activity against DPPH radicals scavenging, phosphomolybdate, and reducing power assay. Also, the results agree with those reported the pronounced DPPH scavenging property of the aqueous extracts of *Arthrospira*/*Spirulina* sp. (Cyanobacteria) and *Nannochloropsis* sp. (Ochrophyta, Eustigmatophyceae) (Figure 4c) [63]. In addition to that the acetone extract of *Chlorella vulgaris* showed antioxidant activity against the all tested assays due to the presence of biologically active metabolites [64]. Recent studies, the microalgae *Nannochloropsis* sp. possessed the higher amount of essential fatty acid and exhibited the potential antioxidant activities for the methanolic extract and proved that the methanolic extract of *Nannochloropsis* sp. would be helpful to prevent the oxidative stress and can be used as a potential natural antioxidant [65]. Additionally, Gheda et al. [57] investigated that the methanol extract of *Arthrospira platensis* exhibited the highest antioxidant activity for all the tested assays (DPPH, reducing power and total antioxidant capacity assays) rather than the other solvents. Moreover, the phytochemical components in the different solvents of the microalgae *Hydrodictyon reticulatum* (Chlorophyta) extracts showed various antioxidant activity against the different assays [66].

For the first time, Moaveni et al. [67] investigated that *Schizochytrium limacinum* (Thraustochytriaceae, Labyrinthulomycetes) could demonstrate a potential source of bioactive peptides with antioxidant activities. Therefore, *S. limacinum* demonstrate interesting properties for nutraceutical pro-duction or used directly as a dietary intervention to prevent diseases associated with free radicals.

Seaweeds contain various inorganic and organic substances which can benefit human health [68]. Marine macroalgae have gained their importance because they can synthesize a wide variation of secondary metabolites, and as source of bioactive compounds such as sulfated polysaccharides, proteins, amino acids, peptides, lipids, minerals, sterols, and pigments and some vitamins, and thus, seaweeds have been known as renewable

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good antioxidant resources due to their capacity to repair oxidative damage caused by ROS and its negative effect [68].

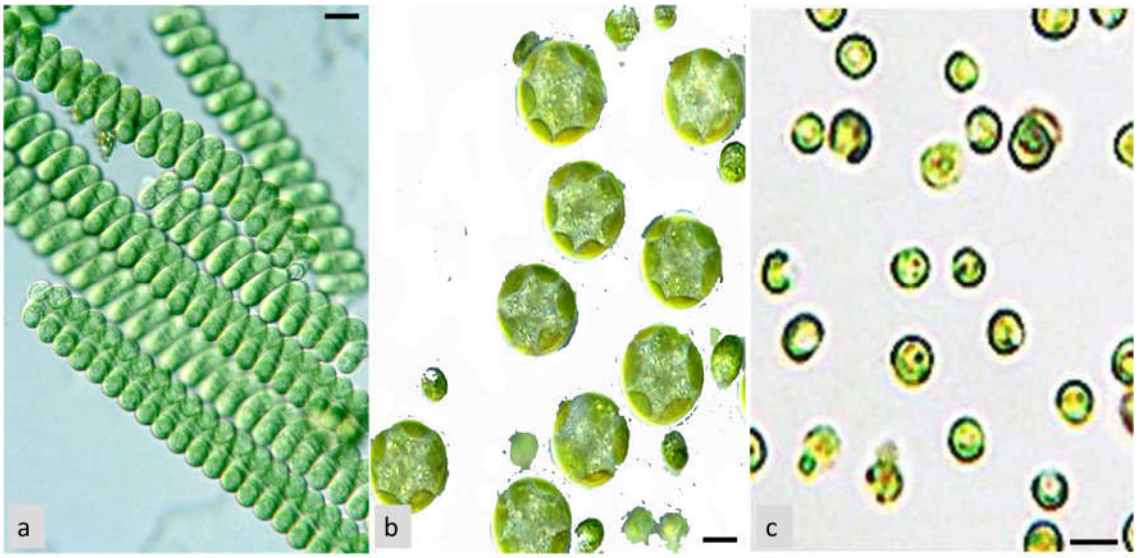

Figure 4. microalgae species images: (a) – *Arthrospira platensis* (Cya); (b) – *Chlorella vulgaris* (Chl); (c) *Nannochloropsis* (Eus); (Cya) - Cyanobacteria; (Chl) - Chlorophyta; (Eus) - Eustigmatophyceae. Scale = 10 μm .

Furthermore, seaweeds possess a high concentration of phenolic molecules, making them one of the greatest sources of natural antioxidants [69]. The expression of the phenolic compound defines several hundred molecules that can be found in fit for human consumption plants that own on their structure a benzenic ring replaced by, at least, one hydroxyl group [70]. Phenolic compounds can act as antioxidants through chelating the metal ions, avoiding radical formation and enhancing the antioxidant endogenous system [71]. In this connection many studies investigated the antioxidant activity of the different macroalgae. Firstly, the methanolic extract of the alga *Centroceras clavulatum* (Rhodophyta) exhibits high antioxidant activity with all the tested assays [70]. *In vitro* DPPH, ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), and FRAP (fluorescence recovery after photobleaching) antioxidant assays of the methanol extract from *Ulva lactuca* (as *Ulva fasciata*) (Chlorophyta) (Figure 5a), showed an outstanding ROS-scavenging potential [72].

Furthermore, Unnikrishnan et al. [28] concluded the antioxidant activity of the ethyl acetate extract of *Sargassum polycystum* and the acetone extract of *Sargassum wightii*. In addition, the antioxidant analysis showed that *Fucus spiralis* (Ochropyhta, Phaeophyceae) (Figure 5b) protein hydrolysate-ultrafiltrate fractions FSPH-UF exhibited significantly higher scavenging of DPPH radical, ferrous ion-chelating (FIC) activity, also had notably higher ferric reducing antioxidant power (FRAP), and this is due to the bioactive peptides and polyphenols released during the enzymatic hydrolysis [73].

Too, the results from the study of Vijayan et al. [74] clearly demonstrate that *Sargassum wightii* (Ochrophyta, Phaeophyceae) fraction, obtained by extraction of *S. wightii* using ethyl acetate, showed antioxidant activity using DPPH, and ABTS, as well as Ferric, Reducing Antioxidant Power (FRAP). Also, the methanolic extract of the brown algae *Turbinaria decurrens* contain a high concentration of polyphenols and exhibited broad spectrum of antioxidant activity by showing potent radical scavenging activity against 2-Azino-bis diammonium salt (ABTS) and 2-diphenyl-1-picrylhydrazyl (DPPH) free radicals, as well as high reducing capability of copper ions [75].

Moreover, in the study of Ismail et al. [76] they showed that among the tested extracts, acetone extract of *T. decurrens* showed the highest antioxidant effect using DPPH, reducing power and total antioxidant capacity assays. In addition to that, the data of El-Sheekh et al. [77] displayed that ethanol extract of the brown algae *Taonia atomaria* (Figure

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5c) has recorded the highest antioxidant potential with the various tested assays. The methanolic extract of *Padina pavonica* (Ochrophyta, Phaeophyceae) (Figure 5d) established the highest DPPH radical scavenging activity (55.7% ± 0.1) at 50 µg/mL [78].

Likewise, the results of the investigation of Abhishek et al. [79] demonstrated that methanolic solvent were successful for extracting polyphenols from *Padina boryana* (Ochrophyta, Phaeophyceae) which is strongly correlated with its antioxidant activity. The enzymatically degraded polysaccharide (ESFP), from brown algae *Sargassum fusiforme*, prepared in this investigation, possessed superior antioxidant on scavenging $HO^{\cdot}$, O_2^{-} and $DPPH^{\cdot}$ [80]. In addition to that, the freeze-dried samples of the brown *alga Padina pavonica* extracted with ethanol had the higher antioxidant activity with hydrogen atom transfer (HAT) (DPPH and ORAC) and electron transfer (ET) (FRAP) [81].

Additionally, the ethyl acetate fraction from the red seaweed *Laurencia dendroidea* had the highest antioxidant activity when evaluated by the DPPH radical scavenging assay (IC50 value of 312.09 µg/mL) [82]. Moreover, the results of El Nur et al. [83] indicated that the ethanol extract of *Jania rubens* (Rhodophyta) (Figure 5e) exhibited the most potent antioxidant crude extract with 86%. Likewise, The investigation revealed that the methanolic extract of the red alga *Pterocladiella capillacea* (Figure 5f) possesses large amounts of total polyphenols, which are responsible for its antioxidant potential [84]. Moreover, the methanolic extract of *Chondrus crispus* (Rhodophyta) (Figure 5g), obtained from the Red sea, was found to contain several flavonoids, polyphenols and tannins which displayed remarkable antioxidant activity [85]. The same found in the results of Murugesan et al. [86], the methanol extract of the red seaweed *Ahnfeltiopsis pygmaea* (formerly *Gymnogongrus pygmaeus*) can be valuable source of antioxidants to cure diseases oxidizing diseases.

3.4. The inhibitory activity of algae on the carbohydrate hydrolyzing enzymes

A regular consumption of functional foods appears to be associated with improved antioxidant enzymes, suppress over production of proinflammatory cytokines, insulin sensitivity, and hypocholesterolemia functions, which are considered essential to preventing and controlling T2DM. There have been indications that algae could be used as antidiabetic foods/ingredients, but the mechanisms of action remain unclear [87,88].

In this connection, Gouda et al. [61] reported that inhibition of α-glucosidase activity by *Spirulina* butanol extract with an IC_{50} of 23 µg/mL. In addition to that, the data of Priatni et al. [89] shown that the highest activity in inhibition of α-glucosidase was exopolysaccharides from *Pseudanabaena* sp. (Cyanobacteria) (14.02%) among the other microalgae. Not only that but also aqueous and methanolic extracts of microalgae *Euglena cantabrica* (Euglenozoa) also exhibited the highest antioxidant activity which is due to the presence of the high contents of phenolics [90]. Results of the study of Ahmed et al. [91] revealed that *Fischerella* (Cyanobacteria) BS1-EG aqueous extract exhibited potential activity in alpha-glucosidase inhibition, i.e., 7.5%, indicating its anti-diabetic effect. Also, Fucoxanthin extracted from *Phaeodactylum tricornutum* (Bacillariophyta) displayed strong hindrance activities toward α-amylase in a concentration-dependent manner, with an IC_{50} value of 0.68 mmol/L, and inhibitory activity against α-glucosidase, with an IC_{50} value of 4.75 mmol/L [92]. Likewise, ethyl acetate extract of *Nannochloropsis oculata* (Ochrophyta, Eustigmatophyceae) exhibited the highest level of α-amylase inhibition of about 78.52% at 1000 µg/mL, and the IC_{50} was found to be 121.96 µg/mL. The same extract exhibited a significant inhibitory action on the α-glucosidase enzyme of 80.42% with an IC_{50} of 178.53 µg/mL at the concentration of 1000 µg/mL [93].

Recently, findings were recorded by Gheda et al. [57], who found that the methanolic extract of *Arthrospira platensis* exhibited the maximum α-amylase enzyme inhibition activity of 96.46% with an IC_{50} value of 13.31 mg/mL compared to Acarbose standard drug which recorded 1.59 mg/mL. The same extract was also found to have a strong α-glucosidase inhibitory activity of 97.42% and an IC_{50} value of 9.56 mg/mL compared to Acarbose standard drug, which recorded 1.03 mg/mL. Moreover the results of Priatni et al. [94]

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showed that the methanolic extract of the marine microalgae *Porphyridium* sp. (Rhodophyta) is the best microalgae in the inhibiting of α-glucosidase enzyme with 12.63%.

On the same context, seaweeds contain various inorganic and organic substances which can benefit human health [95]. Because of their ability to synthesize a wide range of secondary metabolites and as a source of bioactive compounds such as sulfated polysaccharides, proteins, amino acids, peptides, lipids, minerals, sterols, pigments, and some vitamins, seaweeds have become known as renewable good sources of antioxidants due to their ability to repair oxidative damage caused by ROS and its harmful effect. Furthermore, because seaweeds have a high concentration of phenolic molecules, they are regarded as one of the greatest sources of natural antioxidants. [96]. The expression of the phenolic compound defines several hundred molecules that can be found in fit for human consumption plants that own on their structure a benzenic ring replaced by, at least, one hydroxyl group [97]. Phenolic compounds can act as antioxidants through chelating the metal ions, avoiding radical formation and enhancing the antioxidant endogenous system [60]. For that, The study of Reka et al. [98] reported that the solvent from ethanol of *Ulva reticulata* (Chlorophyta) showed a maximum of 89.1 and 79.55% of α-amylase and alpha-glucosidase inhibition activity. Moreover, different green seaweed extracts such as *Ulva intestinalis* (as *Enteromorpha intestinalis*) (Figure 5h), *Chaetomorpha aerea* (Figure 5i), and *Cladophora rupestris* (Chlorophyta) (Figure 5j) proved their activity to manage the diabetes by inhibiting the digestive enzymes related to it [99]. Mohapatra et al. [100], reported the antidiabetic properties of the ethyl acetate extract of *Ulva lactuca* (as *U. fasciata*) green seaweed by inhabiting of the diabetic enzymes due to their antioxidant activity. In addition, the extracts of the ethyl acetate extract of *Sargassum polycystum* and the acetone extract of *Sargassum wightii* have significant effects in inhibiting α-amylase (IC_{50} 438.5 μg/mL)and α-glucosidase (IC_{50} 289.7 μg/mL) and thus can prevent postprandial hyperglycemia [28]. Also, the methanolic extract of brown *alga Spatoglossum asperum* showed a significant α-glucosidase inhibitory activity due to the presence of phytochemicals such as flavonoids, tannins and saponins [101].

The data of the investigation of Osman et al. [102], the methanolic extract of the brown seaweed *Hormophysa cuneiformis* was the most active species for antidiabetic activity that reached to 53% inhibition of α-glucosidase at the highest concentration (1000 μg/mL) with IC50 676.9 μg/mL. Additionally, a semi-purified phlorotannin fraction of *Fucus vesiculosus* (Ochrophyta, Phaeophyceae) (Figure 5k) shows promising inhibitory effects, particularly against the enzymes related to the diabetes α-amylase and α-glucosidase for which a greater inhibitory effect was observed compared to the pharmaceutical drug acarbose (IC_{50} = 2.8 and 0.82 μg/mL, respectively, against 206.6 μg/mL) [103].

Also, the study of Arguelles and Sapin [75], exhibited that the in vitro study of α-glucosidase inhibition showed that the methanolic extract of brown macroalga *Turbinaria decurrens* has potent inhibitory activity (IC_{50} of 11 μg/mL), as compared to that of acarbose and metformin (antidiabetic drugs). Besides, the acetone extract of the brown algae *T. decurrens* showed the highest inhibitory effects for the diabetic enzymes α-amylase (96.1%) with IC_{50} value of 4.37 mg/mL and α-glucosidase (97.4%) with an IC_{50} value of 2.84 mg/mL, which was related with its total phenolic content and antioxidant activity [76]. Among the selected seaweed extracts, the ethanol extract of *Taonia atomaria* (Figure 5c) demonstrated the maximum α-amylase inhibition capacity (66.3% ± 0.0) [78].

Additionally, Tessema [104] informed the inhibitory activity of the protein extraction from the red alga *Porphyra* sp. (Figure 5l) on the diabetic enzymes α-amylase and α-glucosidase. Besides, the ethyl acetate fraction from the red seaweed *Laurencia dendroidea* showed potent antidiabetic activity as it had strong in vitro α-glucosidase inhibitory with IC_{50} value of 8.14 μg/mL [82]. Similarly, the result of the study of Sanger et al. [105] concluded that various phytochemical constituents detected in water extract of the red alga *Halymenia durvillei* which responsible for the antidiabetic potential to inhibit α-glucosidase enzyme activity (IC_{50} 4.34 mg/mL).

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3.5. In vivo antihyperglycemic activity of algae

Administration of cyanobacteria leads to regaining body weight in Streptozotocin (STZ)-induced diabetic rats and reverses the hepatic damage by renormalizing of serum hepatic marker enzymes. Also, cyanobacteria show anti-hypoglycemic action through potentiation of pancreatic secretion of insulin from the intact beta cells of the islets. In a recent study, diabetic rabbits, when fed with *Arthrospira platensis* (Cyanobacteria) powder, showed antihyperglycemic activity by lowering their blood glucose levels [106]. Moreover, the administration of 400 mg/Kg of *A. platensis* powder could reduce the adverse effect of hyperglycemia in the alloxan-induced diabetic rats [107]. Besides, the antioxidants compounds detected in *A. platensis* extract can aid to prevent diabetes or alleviate its adverse effects on blood parameters and the inflammatory phase [108]. In a study conducted by Gheda et al. [57], diabetic rats which has given *A. platensis* methanol extract showed a significant reduction in high glucose levels, liver functions, renal functions, total bilirubin, and lipid profile. In addition, compared to the diabetic control group of rats, caused a regain in body weight loss, protein profile, albumin, hemoglobin, and HDL levels. The same extract improved the histological tissue damage induced by diabetes induction in the liver and pancreatic tissues of the treated rats without creating any negative effects.

Moreover, for green microalgae, the effects *Chlorella vulgaris* supplement as an antioxidant and on the hematological parameters of diabetic rats has been detected [109]. The study of Kawee-Ai et al. [92] reported the antidiabetic property of *Phaeodactylum tricornutum* fucoxanthin extract. Likewise, Nasirian et al. [110] investigated that the oral administration of *Nannochloropsis oculata* microalgae was able to reverse the negative effect of STZ induction by reducing lipid profile and glucose except HDL-C, and increasing insulin and HDL-C in diabetic rats. It also controlled body weight in diabetic rats. These potential effects may be attributed to some components present in microalgae such as fibers, lipid profile and antioxidant pigments.

Many studies documented the biological properties of green seaweeds. In a complementary study by Mohapatra et al. [111], the authors endorsed the ability of the *Ulva lactuca* (as *U. fasciata*) ethyl acetate extract to be used as additive therapy during diabetes treatment and reverse the complications related to diabetes as being non-toxic to important tissues. Correspondingly, the aqueous extracts of *Ulva reticulata* possessed an inhibitory property of the enzymes associated with diabetes [98]. A promising protective effect of *U. reticulata* against diabetic complications generated by STZ-mediated oxidative stress was reported [112]. Diabetic rats treated with ethanolic extract of the green macroalgae *U. reticulata* as oral administration for 45 days resulted in a significant reduction in fasting plasma glucose, TBARS, and lipid hydroperoxides. Besides, using this extract elevated the activities of plasma insulin, vitamin E, and vitamin C and reduced glutathione (GSH) when compared with the diabetic control group. A study by Labbaci and Boukortt [113] indicated that consumption of the green alga *Ulva lactuca* and its hydroethanolic extract mitigate insulin resistance, which plays a fundamental role in the pathogenesis of diabetes and may help regenerate damaged pancreatic β-cells. In addition, *U. lactuca* and its hydroethanolic extract may have anti-atherosclerotic effects by improving reverse cholesterol transport. Such results may have major therapeutic promise for helping to prevent the onset of complications in diabetic patients.

Many research works reported that most of the brown algae are rich in important secondary metabolites which are reported to have an *in vivo* antidiabetic activity [114]. For example, Na-alginate from *Turbinaria ornata* exhibited antihyperlipidemic and antidiabetic activities through the reduction of blood glucose and other diabetic-boosted physiological changes [115]. It was reported in recent studies that, aqueous extract of *Padina boergesenii* brown seaweed was found to have a vital effect on the reduction of blood glucose, the elevated levels of kidney markers and liver function lipid profile in addition to its hepatoprotective activity [116,117].

In a complementary study by Mohapatra et al. [111], they investigated the ability of the ethyl acetate extract from *Sargassum wightii* brown seaweed as an additive therapy

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during diabetes treatment and to reverse the complications related to diabetes as being non-toxic to important tissues. Likewise, Pirian et al. [14] determined the antidiabetic and antioxidant potential of the methanolic extracts for both *Polycladia myrica* (Figure 5m) and *Sirophysalis trinodis* (Ochrophyta, Phaeophyceae). In addition, the pre-prandial administration of the brown alga *Ascophyllum nodosum* extract was able to control the hyperglycemia of diabetic animals [118]. The same effect was observed in the brown alga *Sargassum hystrix* extracts at a dose of 300 mg/kg. This extract was able to lower the levels of preprandial and postprandial glucose of STZ-induced diabetic rats and reversed the weight of rats, triglycerides, and cholesterol levels to their normal (control) levels. Moreover, this dose had the best capability to prevent necrosis of the pancreas in diabetic rats [119]. The data of Akbarzadeh et al. [120] mentioned that the hydroalcoholic extract of the brown macroalga *Sargassum oligocystum* at a dose of 300 mg/kg has a healing effect on diabetes by reducing insulin resistance, decreasing glucose concentration and triglyceride, and regeneration of pancreatic damaged β-cells in STZ-induced diabetic rats.

Recently, an *in vivo* investigation conducted by Abdel-Karim et al. [121] revealed that oral administration of rats with *Turbinaria decurrens* AE at 300 mg/Kg dose exhibited antihyperglycemic activity against alloxan-induced diabetic rats by reducing the elevated blood glucose level, remarkably decreasing the liver and kidney functions, and reducing the hyperlipidemia related to diabetes. In addition, as compared to untreated diabetic rats, treatment of the same extract resulted in a recovery in body weight loss, total protein, albumin, and hemoglobin levels. Furthermore, treatment of rats with the same extract alleviated diabetes-related liver and pancreatic histopathological abnormalities.

Concerning the biological activities of red seaweeds, Murugesan et al. [122] documented the antidiabetic activity of the red alga *Grateloupia lithophila* methanolic extract, which could inhibit the diabetic enzymes α-amylase and α-glucosidase. Radhika and Priya [123] revealed that ethanol extract of the red alga *Acanthophora spicifera* was able to reduce blood glucose levels and the hematological and biochemical parameters linked to diabetes and was able to improve the loss in body weight as well. In the same manner, the red alga *Gelidium amansii* controlled diabetes of STZ-induced diabetic rats via reducing their plasma glucose level, lipids, adipocytokines, and adipose tissue weight [124]. The efficacy of sulfated galactopyran compound from *Gracilaria opuntia* against diabetes and the histological changes related to it was reported by Rayapu et al. [125]. Also, the aqueous extracts of *Gracilaria edulis* possessed an inhibitory activity of the enzymes related to diabetes [98]. *In vivo* results of the study by Nguyen et al. [82] revealed that the ethyl acetate fraction of the red seaweed *Laurencia dendroidea* could significantly suppress the glucose level of alloxan-diabetic mice and the oral administration of the same extract did not exhibit toxicity at a dose of 100 mg/kg body weight as determined by body weight changes and liver biochemical parameters.

3.5.1. Effect of algal treatment on the blood glucose levels of diabetic-induced animals

In a recent study, diabetic rabbits, when fed with *Arthrospira platensis* powder showed antihyperglycemic activity by lowering their blood glucose levels [106]. Moreover, the administration of *A. platensis* powder (400 mg/Kg) could reduce the adverse effect of hyperglycemia in the alloxan-induced diabetic rats [107]. In their study, El-Baz et al. [126] informed that the possible mechanism by which *Arthrospira/Spirulina* brings about its antihyperglycemic action may be through improving the pancreatic secretion of insulin from β-cell islet or due to enhancing the transportation of blood glucose to the peripheral tissue. This was clearly demonstrated, according to the former study results, by the increased levels of insulin in the diabetic rats treated with *Arthrospira/Spirulina*.

Through the same behavior, the increase in postprandial blood glucose level was significantly suppressed by *Turbinaria decurrens* acetone extract administration (300 mg/Kg body weight) in the diabetic rats. These findings suggested that *T. decurrens* acetone extract might slow the absorption of dietary carbs, hence preventing a rise in postprandial

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blood glucose levels. In a previous study, brown algae extract was shown to have a beneficial effect in controlling postprandial glucose levels in diabetic obese rats [127].

Likewise, *Sargassum ringgoldianum* methanolic extract [33] and *Padina boergesenii* (Ochrophyta, Phaeophyceae) aqueous extract [116] demonstrated a decrease in blood glucose levels in STZ-induced diabetic mice. Likewise, the therapy with brown seaweeds "*Sargassum longiotom* Selvaraj & Palanisamy" ethanolic extract [128] and with *Hydroclathrus clathratus* aqueous extract [129], it shown anti-hyperglycemic activity in alloxan-induced diabetic rats. Furthermore, *Turbinaria ornata* has a strong effect in lowering blood glucose levels in alloxan-induced diabetic rats, which was been demonstrated by the study of Husni et al. [115].

Mohapatra et al. [111] demonstrated that the oral treatment of diabetic rats with ethyl acetate extracts of *Sargassum wightii* and *Ulva lactu*ca (as *U. fasciata*) shown remarkable effectiveness in lowering elevated glucose levels. In this regard, one putative mechanism by which such extracts exert anti-hyperglycemic effect in diabetic rats is by increasing glucose transport across cell membranes and boosting glycogen formation, or by enhancing glycolysis pathway via degranulation in pancreatic β-cells [116]. Furthermore, these extracts may have insulin-like effects on peripheral tissues, either by promoting glucose absorption, lowering glucose uptake in the gut, and/or blocking hepatic gluconeogenesis. [123].

3.5.2. Effect of algal treatment on the body weight of diabetic-induced animals

Alloxan-induced diabetes is accompanied by gradual body weight loss, which might be owing to increased muscle wasting or protein breakdown in the tissues [130]. The rats' diabetes state is frequently associated to a drop in body weight.

Layam and Reddy [131] informed that the oral handling of diabetic rats with *Spirulina* powder at different doses resulted in an increment in their body weights. However, many studies reported similar findings. Pandey et al. [132] stated that the rats with diabetes treated with *Limnospira maxima* (formerly *Spirulina maxima*) showed an increase a regain in their body weight which may be well explained by the increased insulin secretion or the increased food consumption. Likewise, oral administration of *Arthrospira platensis* aqueous extract to the diabetic rats for 50 days led to an obvious increase in their body weight, suggesting that this extract substantially improved the general health status and metabolic mechanisms by effective glycemic controlling or reversing of gluconeogenesis [133]. In addition to that, Hussaini et al. [107] reported that the administration of 400 mg/Kg powder of *A. platensis* could significantly reduce the adverse effect of body weight loss in the diabetic rats inducted with alloxan showing a significant enhancement in body weight loss when compared to diabetic control rats. Similarly, the diabetic rabbits, when fed with *A. platensis* powder, showed a noteworthy increase in their lost body weight [106]. Also, Gheda et al. [57] informed that a significant increment in the body weight of alloxan-induced diabetic rats was recovered by taking different oral treatment doses of *A. platensis* as methanol extract compared to the diabetic control (untreated) rats.

In the same manner, Nagy [129] demontrated the ability of aqueous extract of *Hydroclathrus clathratus* (brown seaweed) to restore body weight loss caused by diabetes induction in mice. The ethanol extract from different seaweeds *Acanthophora spicifera* (Rhodophyta), *Caulerpa scalpelliformis* (Chlorophyta), and *Padina tetrastomatica* (Ochrophyta, Phaeophyceae) improved the loss of the body weight in the diabetic rats [123]. Moreover, Mohapatra et al. [111] demonstrated that oral therapeutic of ethyl acetate extracts of *Sargassum wightii* and *Ulva lactuca* (as *U. fasciata*) in the diabetic rats emonstrated considerable activity in improving body weight loss. Likewise, Abdel-Karim et al. [64] found that administration of *T. decurrens* acetone extract (AE) or standard Diabenor drug tended to reverse the loss of body weight due to the induced diabetic effects but untreated diabetic mice had a significant decrease in body weight.

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3.5.3. Effect of algal treatment on the hemoglobin (Hb) levels of diabetic-induced animals

Many studies verified that the hemoglobin level is affected by the presence of glucose in the blood. Layam and Reddy [131] explained that the improvement in the level of Hb in animals supplemented by different doses of *Arthrospira* might be due to the decreased level of blood glucose that automatically led to decreased Hb values. Another reason is that *Arthrospira*, which is a respectable source of iron, might be contributed to raising of the Hb levels. In a recent study, diabetic rabbits, when fed with *A. platensis* powder, showed a repairing of the Hb decreased values [106]. According to the study conducted by Gheda et al [57], the Hb value was found to be considerably lower following alloxan-induced diabetes. A substantial increase in Hb levels was seen in diabetic rats after treatment with various doses of *A. platensis* extract.

In the same context, Banu and Mageswari [134] demonstrated the green seaweed *Ulva reticulata* was shown to have a therapeutic impact in addressing iron deficiency and boosting Hb levels. Thus, it was discovered that these seaweeds may aid to improve iron status through simple absorption by the body. Furthermore, treatment *with Turbinaria conoides* ethanolic extract and *Sargassum wightii* and *T. conoides* methanolic extract resulted in a rise in Hb level, which was related with a descent in blood glucose level [125]. Furthermore, treatment with *Padina boergesenii* aqueous extract increased Hb levels in diabetic rats significantly [117]. Likewise, the increase in Hb levels might be occurred owed to the enhanced glycemic control along with the decrease of glucose level produced by *Turbinaria decurrens* extract treatment which was, in turn, directly proportional to glycosylated Hb level [121]. In contrast to these results, Radhika and Priya [123] discovered that after inducing the rats with alloxan, the Hb level increased, and that treating these diabetic rats with seaweeds might lower it.

3.5.4. Effect of algal treatment on the total bilirubin of diabetic-induced animals

Bilirubin concentrations may reflect the state of the liver and the sort of damage done to it [135]. According to Dey et al. [136], improved hepatic function was caused by lower levels of free fatty acids and associated peroxides in the blood, as well as lower levels of oxidation and hepatic inflammation. The possibility of restoring liver-execratory function in diabetic rats may be due to the administration of *Aphanizomenon flos-aqua* (Cyanobacteria) ethanolic extract and insulin-like protein [137]. According to the study conducted by Gheda et al. [57], the bilirubin value was expressively amplified after prompting diabetes with alloxan in rats. The total bilirubin value of diabetic rats treated with the different doses of A. platensis methanolic extract exhibited a significant reduction. Similarly, the incensement in the total bilirubin level in the diabetic control rats was diminished following oral administration of various dosages of *T. decurrens* extract as reported by Abdel-Karim et al. [121].

3.5.5. Effect of algal treatment on the liver enzymes of diabetic-induced animals

The levels of aminotransferase enzymes, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) [138], are a primarily valuable aid in the diagnosis of liver disease as being liver toxicity markers [139] and also were reflecting hepatocellular necrosis [140]. In earlier studies, the increment of aminotransferase enzyme activities under deficiency of insulin was reported to be responsible for the increased ketogenesis and gluconeogenesis during diabetic disorders [141]. Changes in serum enzymes in diabetic rats were closely connected to changes in metabolic function of both AST and ALT enzymes. [142]. The mechanism by which blood levels of both aminotransferases were higher in diabetic rats may entail increased release of these enzymes from organs, primarily the liver, as a result of oxidative stress or the production of progressive glycosylation end products, as well as liver dysfunction [139]. As reported by Ohaeri [143], in induced diabetic rats, liver tissue necrotized. As a result, an increase in ALT and AST activity in the

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serum might be due to these enzymes escaping from the cytosol of the liver into the bloodstream, indicating a hepatotoxic impact in the induced diabetic rats. As a diabetic inducer, alloxan injection was toxic and had a detrimental effect on hepatic tissues, which was followed by an increase in AST and ALT enzymes [57,133]. This observed effect may be attributed to the hepato-protective properties of A. platensis because its extract exhibited anti-inflammatory, antioxidant, membrane-stabilizing, and immune-correcting actions as recommended by Panigrahi et al. [144]. These outcomes were also supported by those mentioned by El-Baz et al. [126] who reported that A. platensis ethanolic extract could reduce AST and ALT levels. Also, Salem et al. [145] investigated the therapeutic effect of *A. platensis* powder and informed reduction of the hepatic enzyme activities.

Similarly, dietary supplementation of diabetic rats with *A. platensis* powder showed a significant beneficial effect by reducing serum hepatic AST and ALT as compared with the control negative rats [146,147]. In addition, Ripa et al. [106] documented the potent activity of *A. platensis* powder for the reduction of the raised levels of hepatic enzymes in diabetic rabbits. After administration of *A. platensis* extract as treatment, a decrease of the serum ALT and AST activities might subsequently imply alleviation of the liver damage. The treatment of 15 mg/Kg BW of *A. platensis* extract was significantly potent in the reduction of hepatic transaminase activities comparable to the alloxan-diabetic control rats [57].

Furthermore, some studies investigated the effect of macroalgae as reducer agents for hepatic enzymes. Selvaraj and Kumar [128] suggested that "*Sargassum longiotom* Selvaraj & Palanisamy" *nom. Inval.* ethanolic extract may prevent hepatic injury associated with diabetes. The extract could reduce the levels of serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), which are marker enzymes reflecting the necrosis of the hepatocellular by liberating into the bloodstream after damaging of the cell membrane, as well as, oral administration of *Hydroclathrus clathratus* aqueous extract resulted in a significant reduction in hepatic enzyme levels. [129]. In accordance with that, Dey et al. [136] mentioned the amelioration of hepatic transaminases resulted because of the reduced content of free fatty acids and their peroxides in the serum, as well, the reduced oxidation and hepatic inflammation. Similarly, Abdel-Karim et al. [121] reported that alloxan-diabetic rats treated with *Turbinaria decurrens* acetone extract could considerably compact the two parameters of ALT and AST levels in the blood serum, indicating liver functions recovery.

3.5.6. Effect of algal treatment on the urea and creatinine of diabetic-induced animals

The most often used test for screening renal functions is blood urea determination. When combined with creatinine readings, it can help in the differentiation of three kinds of azotemia (abnormally high levels of nitrogen-containing compounds in the blood). Because the increased creatinine and urea levels represented a decrease in the glomerular filtration rate, the alloxan-induced diabetic rats demonstrated renal impairment. Thus, according to Kumar et al. [116], this was the leading cause of end-stage renal failure, which necessitated dialysis or a kidney transplant..

It has been reported that alloxan caused a considerable increase in serum urea and creatinine. In kidney tissue, alloxan increased the production of reactive oxygen species, increased protein carbonylation and lipid peroxidation, and lowered intracellular antioxidant defense [148]. As suggested by Khan et al. [149], *A. platensis* extract exhibited a nephron-protective effect against diabetic-induced nephropathy. Likewise, Avdagić et al. [150] reported that *Arthrospira/Spirulina* could decrease lipid peroxidation and elevate the antioxidant levels, thus considerably modifying renal damage. El-Baz et al. [126] reported the potent activity of *A. platensis* ethanolic extract in reducing urea and creatinine levels to reach 31.00 and 0.96 mg/dl, respectively, when administrated to the diabetic-induced rats. Also, Abbas et al. [146] reported the good effect of *Arthrospira/Spirulina* for the decrement of urea and creatinine levels. As explained by Ripa et al. [106], this mitigation effect may

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be due to the potential antioxidant properties of *A. platensis* extract that improved the renal function via attenuation of the oxidative stress-mediated decline in kidney function. The same observations were informed by Gheda et al. [57], where the elevated levels of urea and creatinine were significantly reduced to the standard levels in the alloxan-induced diabetic rats after the treatment with different dosages of *A. platensis* methanolic extract.

With similar behavior, Nagy [129] reported a significant reduction in urea and creatinine serum values after oral administration of *Hydroclathrus clathratus* aqueous extract. The brown seaweed *Padina boergesenii* water extract lowered elevated levels of urea, uric acid, and creatinine in diabetic rats [117]. According to Abdel-Karim et al. [121], oral treatment of alloxan diabetic rats with T. decurrens extract has a favorable impact as a considerable decrease in blood urea and creatinine levels, notably at the dose of 300 mg/Kg of body weight.

3.5.7. Effect of algal treatment on the total protein of diabetic-induced animals

During disease, the total protein concentration and percentage denoted by separate fractions could significantly swerve from normal values [151]. Total protein measurements aid in the diagnosis and treatment of diseases involving the kidney, liver, bone marrow, and other nutritional or metabolic problems [152].

The reduction of total protein content linked to diabetes may be as a result of decrease in the three major phases of protein secretion, intracellular transport and discharge, and /or due to an obvious increase in protein excretion [153]. The role of microalgae as biomass or extract to combat the rise in the protein content linked to diabetes. The improvement of protein levels of the diabetic rats treated with *A. platensis* ethanolic extract at a dose of 15 mg/Kg BW was informed by Senthilkumar and John [154]. *A. platensis* ethanolic extract at a dose of 15 mg/Kg of body weight was reported by El-Baz et al. [126] to have a potent activity to improve the decreased protein level related to STZ-induction in the diabetic rats. Also, Salem et al. [145], mentioned that a 15 mg/Kg BW dose of *A. platensis* powder was able to increase the reduced total protein levels as a reverse effect of diabetes. The same enhancement of the protein profile has been observed in the alloxan-induced diabetic rats also treated with 15 mg/Kg BW of *A. platensis* methanolic extract [57]. This improvement might be due to the immuno-stimulatory effect and the antioxidant property of *A. platensis* besides its role in improving the hepatic function and/or its richness of proteins, as explained by Venkataraman [155]. Furthermore, *A. platensis* is composed of numerous amino acids, so it may have become a direct source of protein for mice and produced several beneficial metabolic effects [156].

In the same direction, seaweeds were indorsed with the ability to mitigate the elevation in the total protein content related to diabetes disorders. The upgrading of total protein may be attributable to the marked change in the circulating amino acids level, hepatic amino acids uptake, and muscle output of different amino acid concentrations [157]. This effect may also be due to improvement in either albumin or globulin content or both [158]. Similar outcomes were conveyed by Kumar et al. [116] and Kumar et al. [117], who informed notable improvement in the protein profile after treating diabetic rats with the brown seaweed *Padina boergesenii*, an aqueous extract. Abdel-Raouf et al. [159] reported the potent effect of the brown alga *Hormophysa cuneiformis* ethanolic extract in the promotion of total protein levels. According to Abdel-Karim et al. [121], the decrement of total protein in the induced diabetic rats was significantly improved upon the treatment with *T. decurrens* acetone extract at a dosage of 300 mg/Kg of body weight.

3.5.8. Effect of algal treatment on the albumin level of diabetic-induced animals

Hypoalbuminemia is a prevalent condition in diabetic animals, and it is linked to a decrease in total protein [158]. Diabetes-related hypoproteinemia can be caused by reduced protein synthesis, increased protein breakdown, and/or increased urine protein excretion [160]. As recommended by several studies, the administration of microalgae and

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cyanobacteria may interfere with elevating the albumin level in the blood serum. El-Baz et al. [126] reported that oral administration with 15 mg/Kg of body weight of *A. platensis* ethanolic extract could raise the reduced levels of albumin in diabetic rats. In the study conducted by Salem et al. [145], the treatment of diabetic rats with 15 mg/Kg of *A. platensis* powder exhibited an alleviation of the albumin concentration. Also, Gheda et al. [57] informed of an improvement in the albumin level by treating the diabetic rats with *A. platensis* methanolic extract, though the diabetic control rats exhibited a great reduction in the albumin levels. As previously explained for proteins, the enhancement of albumin level may be induced due to the antioxidant activity and the immuno-stimulatory effects of different algal extracts, which can improve disturbed liver functions [145]. Abdel-Raouf et al. [159] reported a significant increase in serum albumin and globulin levels after co-administered diabetic rats with the ethanolic extract of the brown alga *Hormophysa cuneiformis*. In addition, Kumar et al. [117] suggested the ability of *Padina boergesenii* to treat the albumin reduction effect resulting from diabetes disorders. The same role was evidenced by Abdel-Karim et al. [121], who detected a significant enhancement in the albumin level of the alloxan-induced diabetic rats following oral administration of *Turbinaria decurrens* acetone extract that was indicative of the amelioration of the adverse effects caused by diabetes

3.5.9. Effect of algal treatment on the lipid profile of diabetic-induced animals

Diabetes frequently involves aberrant lipid metabolism in addition to faulty glucose metabolism, which is regarded as an additional metabolic condition in the diabetic compli-cation series. The activation of lipoprotein lipase and lecithin acyl-cholesterol transferases enhanced the concentration of low-density lipoprotein cholesterol (LDL-C). The elevated levels of very-low-density lipoprotein cholesterol (VLDL-C) and triglycerides (TG) were followed by a decrease in high-density lipoprotein cholesterol (HDL-C) [161]. Normally, insulin induces lipoprotein lipase, which hydrolyzes TG. Insulin shortage leads to a lack of enzyme activation, resulting in hypertriglyceridemia (i.e., increased TG levels in the blood) [162]. In the following results, Mir et al. [163] discovered a high content of total lipid in diabetic rabbit blood and ascribed this rise to enhanced mobilization of free fatty acids from peripheral fat depots; in the meantime, insulin protects the sensitive hormone from lipase. Furthermore, the hyperlipidemia reported in diabetic rats might be explained by insulin insufficiency or the oxidative stress associated with diabetes, which can influence lipid metabolism [164]. In this connection, Salem et al. [145] described that the elevated serum levels of TG, total cholesterol (TC), and LDL were decreased in the diabetic rats given 15 mg/Kg body weight (BW) of *A. platensis* powder as well as reversed the effect of the reduced HDL level. This hypolipidemic activity is possibly triggered as a result of phenolic compounds existence in this powder, or due to increase in the activity of lipoprotein lipase enzymes in the muscles while decreasing their activity in the adipose tissues [145]. This also indicated that plasma TG was employed for the energy production by the muscle and not for the storage of energy by the adipose tissue [107]. Similar outcomes were recorded by Gheda et al. [57] through the administration of *A. platensis* methanolic extract in diabetic rats, which caused a significant decrease in serum lipid profile level.

Studies also showed that marine algae contain plentiful bioactive constituents that present a potent ability to reduce cholesterol and blood pressure levels, along with encouraging healthy digestion and antioxidant activity [165]. "*Sargassum longiotom* Selvaraj & Palanisamy" *nom. Inval.* ethanolic extract was recorded to produce a significant beneficial effect on the lipid profile in diabetic rats by reducing TG, TC, and LDL levels and significantly increasing the HDL level [128]. Oral administration of an aqueous extract of *Hydroclathrus clathratus* caused a significant reduction in either the serum TG levels or TC and LDL-cholesterol levels in contrast to a significant elevation in HDL-cholesterol [129]. Similarly, treatment with the ethyl acetate extracts of *Sargassum wightii* and *Ulva lactuca* (as *U. fasciata*) resulted in a lowering of the elevated levels of TG and TC in the diabetes-induced rats [111]. Moreover, the diabetic rats treated with a 400 mg/Kg BW dose of *Padina*

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boergesenii (Figure 5n) aqueous extract reduced the elevated concentrations of TG, TC, and LDL while, increasing HDL levels [117]. Oral supplementation of diabetic rats with *T. decurrens* extract exhibited a significant positive effect on the lipid profile of the diabetic rats induced by alloxan via a significant reduction of TG, TC and LDL levels and increased HDL levels [121].

Figure 5. Seaweed species images: (a) – *Ulva lactuca* (C); (b) – *Fucus spiralis* (P); (c) *Taonia atomaria* (P); (d) – *Padina pavonica* (P); (e) – *Jania rubens* (R); (f) – *Pterocladiella capillacea* (R); (g) – *Chondrus*

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crispus (R); (h) – *Ulva intestinalis* (P); (i) – *Chaetomorpha aerea* C); (j) – *Cladophora rupestris* (C); (k) – *Fucus vesiculosus* (P); (l) – *Porphyra* (R); (m) – *Polycladia myrica* (P); (n) – *Padina boergesenii* (P); (C) - Chlorophyta; (R) - Rhodophyta; (P) - Phaeophyceae. .

3.5.10. Effect of algal treatment on the histological profile of liver and pancreas of the diabetic-induced animals

The liver is critical in the excretion and removal of unwanted chemicals from the body. Characteristic histological findings, showing a liver disease modification, frequently emerged as a result of diabetes induction. The diabetic liver showed hydropic bulging, hepatocyte disarrangement, vacuolization of micro-vesicular with the removal of nuclei, granular disintegration, and necrosis of liver cells. Also, under diabetes conditions, Zhou et al. [166] and Aboonabi [167] informed severe oxidative damage that took place in the liver tissue. Many studies suggested a valuable role for algal extract and/or powder in treating diabetes symptoms, including the hepatic damage effects. In this connection, the effective role of 15 mg/Kg BW of *A. platensis* ethanol extract was described by El-Baz et al. [126] to reverse the hepatic histological changes in the rats resulting from diabetes. Abbas et al. [146] reported that the liver of diabetic rats treated with 200 mg/Kg BW of *Arthrospira/Spirulina* powder showed apparent normal histological structure, except for marked apoptosis of hepatocytes. This recovery effect may be a result of the antioxidant activity of the phenolic compounds present in the powder of *Arthrospira/Spirulina* [168] as well as its proven free radical-scavenging activity [169]. Therefore, according to studies conducted by Abd el baky et al. [170] and Abdel-Daim [171], *Arthrospira/Spirulina* supplementation could act as a potent anti-hepatotoxicity agent. These recommendations were also confirmed by Gheda et al. [57]), who displayed that the liver of alloxan-induced diabetic rats treated with a 15 mg/Kg BW dose of *A. platensis* methanolic extract for 45 days was, most probably, appeared of normal histological structure compared to the untreated control rats.

In the same direction, many studies mentioned the valuable curative role of macroalgal (seaweed) extracts for diabetes and its hepatic complications recovery. The hepatoprotective activity of *Sargassum polycystum* extract against damage to liver tissues was investigated by Motshakeri et al. [43]. Likewise, Nagy [129] reported the positive effect of *Hydroclathrus clathratus* aqueous extract against liver injury due to the induction of diabetes. The treatment with ethyl acetate extracts of *Sargassum wightii* and *Ulva lactuca* (*U. fasciata*) was found to exhibit great improvement in the hepatic morphological and physiological disorders caused by diabetes [111]. The necrosis of hepatic cells, changes in microcellular fats, and wide-ranging vacuolization with the vanishing of nuclei were detected in the diabetic rat liver as observed by Rayapu et al. [125]. These effects were recovered after treatment with different marine algal extracts, viz. *Turbinaria conoides* ethanolic extract, *Sargassum wightii* methanolic extract, along with aqueous extracts of *T. conoides* and *Gracilaria opuntia*.

Kumar et al. [117] reported that *Padina boergesenii* aqueous extract had a protective effect on the injured diabetic rats' livers and reduced the exerted histopathological disorders. Similar findings were informed by Abdel-Karim et al.[121], who endorsed the recovery effect of *Turbinaria decurrens* extract on the diabetic rats' liver after the treatment with 300 mg/Kg BW of this extract.

The pancreas is essential for the control of micronutrient metabolism. As a result, its tissues may be harmed intracellularly during diabetes induction. Due to the lack of visual inspection tools, there is insufficient information on the morphological changes of pancreatic islets with the progression of diabetes [172]. Moreover, any alterations in the systemic metabolism connected to insensitivity, secretion of insulin, and loss of the ability of glycemic control are reflected by alternations in the structure, size, and/or function of the islet [172]. Diabetes has been shown to cause significant histological abnormalities in the characteristic pancreatic Langerhans islets look, vacuolation of islets, inflammation, and capillary dilatation. This is most visible in diabetic control rats, where there is a reduction in

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the size of the islets (atrophy), cellular disintegration, and a decrease in the range inhabited by β–cells [57,173].

In the study by Abbas et al. [146], the authors reported that the pancreas of diabetic rats treated with the powder of *A. platensis* showed hyperplasia in β-cells of the pancreatic tissue and increased the number of Langerhans islets. A. platensis supplementation had a potent activity of free radical scavenging and reduced various indicators of toxicity such as tissue damage in rats as well [174]. The same recommendation was adopted by Aissaoui et al. [173], who reported the beneficial effect *A. platensis* powder to reverse the pancreatic damage observed in diabetic animals. In addition, the histopathological investigation of the pancreas revealed that diabetic rats treated with 15 mg/Kg BW *A. platensis* extract were significantly improved since the histological architecture of the islets appeared with mild vacuolations compared to the diabetic control ones [57].

Considering macroalgae, the antidiabetic activity of *Hydroclathrus clathratus* aqueous extract was documented by Mir et al. [175] in addition to its ability to ameliorate the pancreatic damage induced by alloxan. The ethanol extract *Sargassum polycystum* at 300 mg/Kg BW dose was beneficial in alleviating the histological injuries in the pancreas' tissues of the diabetic animal [43]. These observations also were supported by the results of Kumar et al. [117], who discovered that *Padina boergesenii* aqueous extract had a protective effect on pancreatic tissues, allowing for the restoration of pancreas histological deformations. When compared to Diabenor as the standard medicine, treatment of diabetic rats with *Turbinaria decurrens* acetone extract at 300 mg/Kg BW dosage had a beneficial impact on the wounded architecture of the pancreas and restored it back to normal [121].

In addition to that, the oral administration of normal rats with the different doses of *S. platensis* and *T. decurrens* AE did not display any poisonous effect on the liver tissues when compared to the normal control rats, and the same behavior was detected in the pancreatic tissue for the same extracts *A. platensis* and *T. decurrens* comparing to normal control one. Collectively, these observations were well-matched with our results of the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide tetrazolium) cytotoxicity assay and the biochemical parameters, which proved the safety of both tested extracts with no detected difference in rat parameters compared to the normal control ones.

4. Conclusions

The data described in the literature show the great potential of algae as natural sources of functional ingredients. The study of the chemical composition, in addition to the discovery of the mechanisms of action that involve the biological activities of the different species of algae, will be an interesting source of data for the exploration of new drugs of interest to the pharmaceutical and cosmetic industries, as well as new functional ingredients. for the food industry.

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