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The Potential Therapeutic Effects of Marine Algae (*Ulva lactuca* & *Corallina elongata*) Crude Extracts on Alloxan-induced Diabetic Albino Rats

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ABSTRACT

Diabetes mellitus, a metabolic autoimmune disease caused by the consequences of expanding urbanization on lifestyle, is the third leading cause of death worldwide. However, unpleasant side effects and insufficient glucose control are drawbacks of contemporary diabetic treatment. Due to the undesirable side effects of the currently available antidiabetic drugs, the investigation for an effective natural-based antidiabetic therapy is essential to combating diabetes and its adverse effects. Algae are currently gaining popularity in the pharmaceutical and cosmetic sectors due to their ability to produce a wide range of bioactive compounds. Seaweed extracts have been shown to have promising bioactive molecules with anti-inflammatory, antioxidant, and hypoglycemic effects, making them suitable for the treatment of diabetes. The study aimed to provide valuable insights into the potential therapeutic benefits of marine green algae extracts in the management of diabetes in Alloxan-induced diabetic albino rats. The induction of diabetes in rats occurred intravenously administrated via a single dose of Alloxan at 150 mg/kg b.w. Then, rats were divided into four different groups: negative control group; diabetic control group; diabetic treated group receiving green algae crude extract and diabetic treated group receiving red algae crude extract. Data analysis of the biochemical investigations was performed using appropriate statistical methods to determine the significance of algae extract on diabetic animal models after 6 weeks of treatment. Preliminary results showed that the administration of seaweed (Green and Red Algae) extracts significantly reduced the hyperglycemic, hypercholesterolemia, and hyperlipidemia levels in diabetic-treated rats as compared to the diabetic untreated rats. Based on the above findings, the current research provided antidiabetic activity of marine algae against diabetes and its complications.

INTRODUCTIONS

Diabetes mellitus (DM) is a global health issue, and its incidence is rising all over the world. By 2035, there will be roughly 592 million individuals with diabetes worldwide, up from the current 382 million, according to the International Diabetes Federation **(Jurez-Reyes *et al.*, 2015)**. Numerous biological factors can lead to diabetes, hyperlipidemia, and hyperglycemia are both related to insulin resistance and deficiency

respectively **(Yin *et al.*, 2011; Li *et al.*, 2015)**. However, insulin therapy or oral medications are being currently used as diabetes treatment options for diabetes, focusing primarily on controlling blood sugar levels. But, these treatments often have limitations and side effects. Therefore, there is a need for alternative therapeutic approaches. Traditional treatment options for diabetes include drug interventions, but these are often associated with side effects and limited effectiveness.

Algal biomass has gained global popularity due to its use in a range of industries. The addition of seaweed or its extracts such as alginate and carrageenan as food additives has been found to have important technological implications **(Enzing *et al.*, 2014; Kim & Chojnacka, 2015; Ruiz *et al.*, 2016)**. These hydrocolloids have been found to have many applications in food, pharmaceutical, and other biotechnology fields, as they improve gelation and thicken product texture and maintain stability **(Ścieszka & Klewicka, 2019)**. Algal biotechnology has yielded the discovery of proteins, peptides, amino acids, fatty acids, sterols, polysaccharides, oligosaccharides, phenolic compounds, photosynthetic pigments, vitamins, and minerals **(El Gamal, 2010)**. The bioactive secondary metabolites generated by several metabolic pathways in algae are what give them their unique chemical and biological characteristics **(Abo-Shady *et al.*, 2023)**.

Bioactive molecules and/or compounds derived from algae offer potential health benefits and diverse applications, such as anti-cancer, anti-diabetic, anti-inflammatory, antioxidant, anti-obesity, and neuroprotective **(Alam *et al.*, 2021)**. So yet, nothing is well known about the chemical composition of freshwater algae. Therefore, there is a growing interest in exploring alternative and complementary treatments such as natural products derived from plants and algae. Seaweed is considered a source of various bioactive ingredients and can be considered one of the sustainable food sources. In general, algae can be cultured and produced in brackish or freshwater systems, using a wide range of water types, carbon sources, and nutrient concentrations **(El-Sayed *et al.*, 2022; Abo El-Khair *et al.*, 2023).**

Seaweed possesses various bioactive compounds that potentially exhibit anti-diabetic properties, including antioxidant, anti-inflammatory, and hypoglycemic effects. However, fucosterol is a sterol derived from numerous algae, particularly red and brown macroalgae and is used to help alleviate the side effects of diabetes and high blood pressure. In addition to fucoxanthin, algae produce other carotenoids with antioxidant, anti-cancer, and anti-diabetic effects. Furthermore, it helps to avoid obesity **(Shahidi & Rahman, 2018)**.

***Corallina** elongata* is a species of coralline algae that is extensively dispersed in the North-eastern Atlantic and the whole Mediterranean Sea **(Marchini *et al.*, 2019)**. This species has been recorded in Egypt among other nations, according to the World Register

of Marine Species (2) **(Hind & Saunders, 2013)**. Another species of green seaweed belonging to the Ulvaceae family is called *Ulva lactuca*. Common along the Egyptian Mediterranean shore is *Ulva lactuca*; it may be found in marine and brackish water environments and is extensively dispersed in temperate and tropical climates. Other names for it include edible seaweed, green laver, and sea lettuce **(Abou-Gabal *et al.*, 2022)**. Ulva species provide food, fertilizer, cosmetic agents, medicines, and other ecological and economic advantages. Proteins, lipids, minerals, carbohydrates, alkaloids, saponins, flavonoids, phenols, and quinones are only a few of the biochemical and bioactive components they contain **(Ibrahim *et al.*, 2022)**.

Indeed, algae are a diverse group of photosynthetic organisms that have been studied for their potential health benefits according to the rich bioactive compounds such as antioxidants, polyphenols, and polysaccharides, which have shown promising therapeutic effects in various diseases. However, further research is needed to determine the therapeutic potential of green algae extracts in chronic diseases. Therefore, the study aimed to evaluate the antidiabetic effects of raw green algae extract in rats with alloxan diabetes. However, their potential impact on diabetes and its complications remains largely unexplored.

MATERIALS AND METHODS

Chemicals

Alloxan monohydrate in a lyophilized powder, Catalog Number (2244-11-3) was purchased from Sigma Aldrich company. Alloxan's diabetogenicity is highlighted by its preferential cellular absorption by pancreatic beta cells and subsequent accumulation in these cells **(Szkudelski, 2001)**.

Algae site of sampling

The seaweed samples were collected from the littoral zone in April 2023 from three distinct Alexandria governorate costing sites (Abu-Qir, Al-Mamora, and Al-Amrawy village) at 30 2-4 N and 31 17-19 E (Fig. 2). The red algae, *Corallina elongata*, and the green algae, *Ulva lactuca*, are shown in Fig. (1a, b). Each sample was obtained by hand. The samples were transported to the lab in an ice box filled with salt water to stop evaporation. The algae were then freed of sand fragments and epiphytic pollutants and repeatedly washed in fresh water. The collected species were identified using **Aleem (1993)** procedures, and the Algae Base website was used to validate the identifications **(Guiry, 2013)**.

Preparation of algae crude extract

Specimens of green algae (*Ulva lactuca*) and red algae (*Corallina elongata*) were collected from Alexandria Coast, and identified by the Botany Department, Faculty of Science, Al-Azhar University, Cairo, Egypt. Then, the algae were washed well with tap water and left to dry at room temperature for 2 days. Red algae were decalcified by treating it with 0.5M HCl for 30min at room temperature, followed by washing it with distilled water three times **(Li *et al*., 2021)**. The dry powders of decalcified red algae and green algae (500 g of each) were completely ground and flooded with 1.5L absolute methanol overnight, and then it was filtrated off.

This step was repeated several times for 2 days. Filtrates were collected and evaporated using a rotary evaporator. The condensed solution was lyophilized to obtain the crude extract powder form (120g). The previously obtained powder was soaked in 500ml distilled water for 24h with a mild shaking water bath (500 rpm) at room temperature and then centrifuged at 3000 rpm for 15min to remove the undissolved residues. Afterward, the supernatant was collected, evaporated using a rotary evaporator, and lyophilized to obtain water-dissolved content, which was kept at – 20°C for further examination **(Zaatout *et al.*, 2019)**.

Fig. 1. Photographs of (a): Red algae, (*Corallina elongata*) and (b): Green algae, (*Ulva lactuca*) (b), according to Algaebase **(Guiry, 2001)**

Experimental design

In this study, thirty-two (12 weeks old) adult male albino rats were included. Subjected rats in common were divided into non-diabetic groups and diabetic treatment groups. Diabetic rats were induced by the administration of Alloxan. The diabetic treatment group received daily oral administration of green algae extracts for 6 weeks at 2

different doses, while the control group received a saline solution. The rats were randomly divided into four groups (Each group has 8 rats) as the following:

Group I: Non-diabetic rats (Negative control). Rats were injected intravenously with a single dose of saline solution; a standard diet and tap water.
Group II: Diabetic non-treatment group (Positive control of diabetes). Rats from this group were fasted for 18 hours before induction of diabetes using Alloxan. Diabetes was induced using a single intravenous injection of Alloxan at a dose of 150mg/ kg of body weight **(Dixit & Kar, 2010)**.
Group III: Diabetic treatment group (Alloxan + Algae extract). Diabetic rats were administrated with green algae crude extract at 50mg/ kg of body weight for 6 weeks.
Group IV: Diabetic treatment group (Alloxan + Algae extract). Diabetic rats were administrated with red algae crude extract at 50mg/ kg of body weight for 6 weeks.
Then, rats were daily observed for signs of toxicity; random blood sugar levels were regularly monitored per week throughout the study period. Rats were sacrificed at the end of week 6th post-first week of Alloxan-induced diabetes.

Fig. 2. Location of sampling sites

Dose titration of Alloxan for induction of diabetes

Rats were fasted for 18 hours and allowed free access to water, followed by a single dose (150mg/ kg of body weight, intravenously) of alloxan monohydrate dissolved in sterile normal saline to induce diabetes mellitus in subjected rats. Diabetes was confirmed 48 hours after alloxan injection by determining plasma glucose concentration. The diabetic animals were allowed free access to tap water and a pellet diet and housed in metallic cages at room temperature **(Dixit & Kar, 2010)**. One week later after administration of Alloxan, rats were fasted, and blood glucose levels were determined; the rats with blood glucose levels above 200mg/ dl were considered diabetic and chosen for the experiment, while rats with blood glucose levels outside this range were excluded **(Furman, 2015)**.

Preparation of biological samples

At the end of the 6^{th} week after initiation of treatment, rats were fasted for 12hr, weighed, and blood samples were collected from each animal under diethyl ether anesthesia from retro-orbital venous plexus puncture using blood capillary tubes. The blood samples were collected and then left to clot at room temperature for 15 minutes. Sera were separated by centrifugation at 3000 rpm at 20°C for 15 minutes, where the clear samples were obtained and kept frozen at -80°C for various physiological and biochemical analyses.

Diagnostic biomarkers

All the biochemical measurements were carried out using a spectrophotometer (Labomed 1050, USA). Biochemical analyses included estimation of plasma glucose level; it was enzymatically estimated according to the method of **Dods (2003)**. While, serum insulin level was determined according to the method of **Bürgi *et al.* (1988)** using rat insulin enzyme-linked immunoassay (ELISA) kit (Mercodia AB, Uppsala, Sweden) respectively. Serum triglycerides and total cholesterol levels were determined according to the method described by **Fossati and Prencipe (1982)**; serum HDL-c level was determined according to the spectrophotometric method described by **Warnick and Wood (1995)**, and LDL-cholesterol was calculated according to the following equation, as stated by **Judith *et al.* (1990)**.

Homeostasis assessment to determine insulin sensitivity

The HOMA model is used to yield an estimation of insulin resistance, sensitivity, and β-cell function from fasting plasma insulin and glucose concentrations. The technique is a method for assessing β-cell function and IR from basal glucose and insulin concentrations at the end of the experimental period. HOMA-IR was calculated using the formula FBS (mmol/L) *FI (Mu/ml)/22.5 described by **Muniyappa *et al.* (2008)**, and

HOMA-B was calculated using the formula 20*FI (Mu/ml)/[FBS (mmol/L)-3.5] according to **Ghasemi *et al.* (2015)**.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, version 22) was used in data analysis. Data were expressed as mean ± SE, one-way analysis of variance (ANOVA) test was used to compare between groups. F-probability, obtained from one-way ANOVA, expresses the difference between the groups. This test is used to find a significant difference between more than two groups. *P*- values less than 0.05 were considered significant. Data were tabulated and graphically represented.

RESULTS

1. Glycemic profile

1.1. Glucose and insulin levels

All rats fulfilled the criteria of diabetes after the Alloxan induced-diabetic rat model, as defined by an increase in non-fasting blood glucose level of more than 200 mg/dl on multiple occasions. Moreover, the blood glucose level was measured at baseline in all diabetic treated and untreated groups. In our study, we evaluated the antidiabetic effect of marine green algae as well as red algae extract, respectively, on some parameters of the diabetic state: chronic hyperglycemia, insulin resistance, glucose intolerance, and dyslipidemia in experimental Albino rats.

Alloxan is a uric acid derivative that acts by selectively destroying the pancreatic beta islets leading to insulin deficiency, hyperglycemia, and ketosis. The fasting plasma glucose level results in diabetic-untreated and diabetic-treated rats, respectively, showed a significant increase when compared with the mean corresponding values of non-diabetic rats. However, plasma glucose levels in diabetic rats treated with marine green algae were well, as red algae extract respectively showed a highly significant decrease, compared to the mean values of diabetic untreated rats. Furthermore, serum fasting insulin levels in diabetic-untreated rats and diabetic-treated rats significantly declined, compared to the mean values of non-diabetic rats. Nonetheless, insulin level was significantly elevated in diabetic rats treated with marine green algae as well as red algae extract, respectively, compared to the mean values of diabetic untreated rats.

1.2. Homeostasis assessment model

Subsequently, insulin resistance was assessed by the homeostasis assessment model of insulin resistance (HOMA-IR) and homeostasis assessment model of β cell function (HOMA-β). IR and insulin secretion were calculated with the HOMA method that has been validated against insulin clamp studies. In the state of Alloxan-induced

hyperglycemia, the results showed a significant increase in the serum glucose-to-insulin ratio in the diabetic group, which might be due to the loss of beta-cell function and a severe decrease in insulin secretion. HOMA-IR levels in diabetic-untreated rats and diabetic-treated rats, respectively, showed no significant differences when compared with the mean corresponding values of non-diabetic rats. While, HOMA-IR levels significantly declined in diabetic rats treated with marine green algae as well as red algae extract, respectively, as compared to the mean values of diabetic untreated rats.

However, the βeta cell function (HOMA-β) level showed a significant decrease when compared with the mean corresponding values of non-diabetic rats. Whereas, HOMA-β levels in diabetic rats treated with marine green algae as well as red algae extract, respectively, appeared to a significantly increase as compared to the mean values of diabetic untreated rats.

1.3. Lipid profile

Regarding the lipid profile in our study, alterations were detected in hypercholesterolemia and hyperlipidemia in Alloxan- induced diabetic rats when compared to non-diabetic rats. T. Cholesterol level and low-density lipoprotein cholesterol (LDL-C) level showed no significant differences in diabetic-untreated and diabetic-treated rats, respectively, when compared with the mean corresponding values of non-diabetic rats. In contrast, T. Cholesterol level and LDL-C level in diabetic rats treated with marine green algae as well as red algae extract, respectively, revealed a high significant decrease as compared to the mean values of diabetic untreated rats.

Indeed, there are no significant differences in high-density lipoprotein cholesterol (HDL-C) levels in diabetic-untreated and diabetic-treated groups, compared to the mean values of non-diabetic rats. While, HDL-C levels in diabetic rats treated with marine green algae as well as red algae extract, respectively, revealed a highly significant increase compared to the mean values of diabetic untreated rats. On the other hand, low-density lipoprotein cholesterol (LDL-C) and Triglycerides levels indicated a highly significant elevation in diabetic-untreated and diabetic-treated groups when compared to the mean values of non-diabetic rats. Whereas, LDL-C and triglycerides levels were significantly reduced in diabetic rats treated with marine green algae as well as red algae extract, respectively, compared to the mean values of diabetic untreated rats.

Non-HDL Cholesterol is an estimation of atherogenic lipoproteins and according to recent guidelines is a better risk indicator for cardiovascular disease. The non-HDL cholesterol level showed no significant differences in diabetic-untreated rats and diabetic-treated rats, respectively, when compared with the mean values of non-diabetic rats. Non HDL cholesterol was significantly reduced in diabetic rats treated with marine green

algae as well as red algae extract, respectively, compared to the mean values of diabetic untreated rats.

Table 1. Effect of Marine green & red algae crude extract on fasting blood glucose (mg/dl), insulin (µIU/ml), HOMA-IR, and HOMA-β levels in Alloxan-induced diabetic rats

Parameters / **Groups**	**Glucose (mg/dl)**		**Insulin (µIU/ml)**		**HOMA-IR**		**HOMA-β**	
	Mean ±SE	***P-value***	**Mean ±SE**	***P-value***	**Mean ±SE**	***P-value***	**Mean ±SE**	***P-value***
Group I: (Negative control)	80.0±5.7		13.7±0.9		48.7±4.5		3.7±0.3	
Group II: (Diabetic untreated)	366.8±37.8	***0.001*** [a]	4.9±0.4	***0.001*** [a]	79.5±9.4	***0.001*** [a]	0.3±0.0	***0.001*** [a]
Group III: (Diabetic treatment-Green Algae)	146.8±11.6	***0.05*** [a] ***0.001*** [b]	8.8±0.7	***0.001*** [a] ***0.001*** [b]	57.1±6.1	***0.05*** [b]	1.3±0.1	***0.001*** [a] ***0.001*** [b]
Group IV (Diabetic treatment-Red Algae)	152.5±11.5	***0.05*** [a] ***0.001*** [b]	9.0±0.6	***0.001*** [a] ***0.001*** [b]	60.2±4.9	***0.05*** [b]	1.3±0.2	***0.001*** [a] ***0.001*** [b]
F-Probability	***P<0.001***		***P<0.001***		***P<0.05***		***P<0.001***	

Each value represents a mean of 8 records ± SE.

Means with dissimilar superscript letters are significantly different at $P < 0.05$.

Where: [a] significance at *(P-Value)* vs. negative control group; [b] significance at *(P-Value)* vs. positive control group.

The percentage of changes (%) is calculated by comparing treated groups with negative control.

Table (2): Effect of Marine green & red Algae Crude Extract on serum Total cholesterol, HDL-C, LDL-C, VLDL-C, triglycerides (mg/dl), and Non-HDL-C in Alloxan-induced diabetic rats

Parameters / Groups	T. Cholesterol (mg/dl)		HDL-C (mg/dl)		LDL-C (mg/dl)		VLDL-C (mg/dl)		Triglyceride (mg/dl)		Non-HDL-C (mg/dl)	
	Mean ±SE	*P-value*	Mean ±SE	*P-value*	Mean ±SE	*P-value*	Mean ±SE	*P-value*	Mean ±SE	*P-value*	Mean	*P-value*
Group I: (Negative control)	102±4.9		30±1.4		56±4.5		16±0.7		72±4.2		79±3.4	
Group II: (Diabetic untreated)	186±8.8	***0.001*** [a]	17±1.4	***0.001*** [a]	136±8.1	***0.001*** [a]	33±1.0	***0.001*** [a]	169±8.0	***0.001*** [a]	165±5.0	***0.001*** [a]
Group III: (Diabetic treatment-Green Algae)	103±5.5	***0.001*** [b]	26±2.3	***0.001*** [b]	54±4.2	***0.001*** [b]	22±0.7	***0.001*** [a] ***0.001*** [b]	77±4.4	***0.001*** [a] ***0.001*** [b]	111±3.3	***0.001*** [b]
Group IV (Diabetic treatment-Red Algae)	105±6.9	***0.001*** [b]	29±2.1	***0.001*** [b]	54±7.0	***0.001*** [b]	22±1.0	***0.001*** [a] ***0.001*** [b]	76±7.1	***0.001*** [a] ***0.001*** [b]	110±4.8	***0.001*** [b]
F-Probability	***P<0.001***		***P<0.001***		***P<0.001***		***P<0.001***		***P<0.001***		***P<0.001***	

Each value represents a mean of 8 records ± SE.
Means with dissimilar superscript letters are significantly different at $P < 0.05$.
Where: [a] significance at *(P-Value)* vs. negative control group; [b] significance at *(P-Value)* vs. positive control group.
The percentage of changes (%) is calculated by comparing treated groups with negative control.

DISCUSSION

Diabetes mellitus is a chronic metabolic disease caused by a partial or complete lack of insulin. It leads to inadequate glucose control and acute, chronic complications **(Ikewuchi *et al.*, 2011)**. It is known that in diabetes, there is a change in serum lipid profile that is likely to increase the risk of cardiovascular disease **(Hamden *et al.*, 2009)**. Lowering plasma glucose and lipid levels through diet modification and drug therapy appears to be associated with a reduction in the risk of vascular disease **(de Sousa *et al.*, 2004)**. Alloxan is a uric acid derivative that works by selectively destroying the beta islets of the pancreas, resulting in insulin deficiency, hyperglycemia, and ketosis. Due to its poor stability, relatively shorter half-life, and acidic nature of the solution, intravenous administration of alloxan is preferred **(Srinivasan & Ramarao., 2007)**.

However, some synthetic inhibitors of these enzymes used therapeutically to treat or treat diabetes are sulfonylureas, biguanides, glycosidase inhibitors, insulin, aldose reductase inhibitors, thiazolidinediones, carbamoyl methyl benzoic acid gliclazide, metformin, and acarbose **(Lee *et al.*, 2014)**. Continuous use of these synthetic chemicals should be avoided as it can lead to weight gain, nausea, upset stomach, vomiting,

abdominal cramps, impaired liver function, and bloating **(KWON *et al.*, 2008; Lee & Han., 2012)**. Increasing efforts are being made to find and study potential inhibitors of -glucosidase and -amylase from natural sources to develop compounds for use *in vitro* and *in vivo* as antidiabetic agents without side effects **(Kalita *et al.*, 2018)**.

In the last decades, seaweeds have been considered a large reservoir of bioactive compounds such as bioactive peptides, lectins, carotenoids, polysaccharides, fatty acids, flavonoids, proteins, tocopherols, and phytosterols, with different beneficial properties and potential application in food, cosmetic and pharmacological industries **(Lalegerie *et al.*, 2019).** Due to these compounds, macroalgae present a wide variety of bioactivities, such as antioxidant, anti-viral, anti-fungal, antibacterial, antiproliferative, anti-inflammatory, neuroprotective, adipogenesis and antidiabetic **(Choudhary *et al.*, 2021)**.

The results of fasting plasma glucose levels in diabetic-untreated and diabetic-treated rats, respectively, showed a significant increase when compared with the mean corresponding values of non-diabetic rats. The diabetogenic effects of alloxan are underlined by its selective inhibition of glucose-stimulated insulin secretion via the inactivation of glucokinase and selective necrosis of the beta cells via induced ROS. This view is consistent with the opinion of **Goldner and Gomori (1944)**, who suggested that alloxan-induced hyperglycemia in rats is followed by severe and fatal hypoglycemia, which after several hours yields final hyperglycemia, the last phase of alloxan-induced diabetes.

Nonetheless, plasma glucose levels in diabetic rats treated with marine green algae as well as red algae extract, respectively, figured a highly significant decrease as compared to the mean values of diabetic untreated rats. The results were comparable to that of Fucosterol, which acts by stimulating insulin release thus further confirming that the extract lowers blood glucose by a pancreato-trophic action. Reducing hyperglycemia levels is the furthest functional therapeutic process for the inhibition of pancreatic α-amylase and α-glucosidase, which significantly delays carbohydrate digestion and glucose absorption with smaller consequences than the former diabetic treatments **(Bhandari *et al.*, 2008)**.

Green algae have been found to possess various bioactive compounds that exhibit potential anti-diabetic properties; the administration of green algae crude extract in rats subjected to diabetes may increase the secretion of insulin from beta cells of the pancreas; this increased secretion of insulin stimulates fatty acid biosynthesis and the incorporation of fatty acids into triglyceride in the liver and adipose tissue. Natural products derived from different algal species, such as alkaloids, flavonoids, terpenoids, steroids, and phenols, have received considerable attention over the years due to their diverse pharmacological properties, including their antioxidant and antidiabetic functions **(Paul**

& Yuvaraj., 2013). The findings of **Abo-Shady *et al.* (2023)** described the diverse anti-diabetic effects of bioactive algal components, which are only applicable to *in vitro* and *in vivo* treatments.

The red seaweed, *Corallina officinalis*, is a well-known edible seaweed in many countries and has been accepted as a drug in traditional medicine for over 100 years. Several molecules derived from this red species have demonstrated important antimicrobial anti-inflammatory and analgesic bioactivities (**Yang *et al.*, 2011).** In the current study, methanol extract obtained from *Corallina elongata* is rich in phenolic compounds and exhibited relatively high antioxidant activity. The results revealed that the red seaweed, *Corallina officinalis*, appears to have antidiabetic potential as a source of antioxidant compounds (Phenolic, Condensed Tannin, and Total Flavonoid); they can be used to attenuate the oxidative stress caused by the induction of Alloxan.

Furthermore, serum fasting insulin levels in diabetic-untreated rats and diabetic-treated rats significantly declined compared to the mean values of non-diabetic rats. Nonetheless, insulin level was significantly elevated in diabetic rats treated with marine green algae as well as red algae extract, respectively, as compared to the mean values of diabetic untreated rats. In addition, HOMA-IR levels significantly declined in diabetic rats treated with marine green algae as well as red algae extract, respectively, as compared to the mean values of diabetic untreated rats. However, the βeta cell function (HOMA-β) level showed a significant decrease when compared with the mean corresponding values of non-diabetic rats.

Whereas, HOMA-β levels in diabetic rats treated with marine green algae as well as red algae extract, respectively, appeared to significantly increase as compared to the mean values of diabetic untreated rats. In this regard, one putative mechanism by which such extracts exert an anti-hyperglycemic effect in diabetic rats is by increasing glucose transport across cell membranes and boosting glycogen formation or by enhancing the glycolysis pathway via releasing insulin from degranulation in pancreatic β-cells. The possible mechanism by which marine algae crude extract brings its antihyperglycemic action may be through improving the pancreatic secretion of insulin from the β-cell islet or enhancing the transportation of blood glucose to the peripheral tissue. As a result of insulin insufficiency, the body will be forced to burn fats for energy instead of glucose, resulting in a toxic byproduct called ketones under severe hyperglycemia **(Vasudevan *et al.*, 2013)**.

Furthermore, using this extract elevated the level of insulin when compared with the diabetic control group. This result coincides with that of **Labbaci and Boukortt (2020)** who reported that the consumption of *U. lactuca* seaweed and its hydroethanolic extract mitigated insulin resistance, which plays a fundamental role in the pathogenesis of

diabetes and helps regenerate damaged pancreatic β-cells. In addition, *U. lactuca* and its hydroethanolic extract may have major therapeutic promise for helping to prevent the onset of complications in diabetic patients. Similarly, the administration of *A. platensis* powder (400mg/ kg) could reduce the adverse effect of hyperglycemia in alloxan-induced diabetic rats **(Hussaini *et al.*, 2018)**.

Diabetes is also associated with an alteration in lipid profiles and other biochemical parameters of patients. Regarding the lipid profile in our study, alterations were recorded for hypercholesterolemia and hyperlipidemia in Alloxan-induced diabetic rats when compared to non-diabetic rats. Diabetes frequently involves anomalous lipid metabolism in addition to faulty glucose metabolism, which is regarded as an additional metabolic condition in the diabetic complication 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) **(Valado *et al.*, 2022)**. Furthermore, the hyperlipidemia reported in diabetic rats might be explained by insulin insufficiency or the oxidative stress associated with diabetes that can influence lipid metabolism **(Ebuehi *et al.*, 2010)**. Normally, insulin induces lipoprotein lipase, which hydrolyzes TG. Insulin shortage leads to a lack of enzyme activation, resulting in hypertriglyceridemia **(Shirwaikar *et al.*, 2004)**.

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 **(Cardoso *et al.*, 2015).** The administration of green algae crude extract reduces the elevation of triglycerides, total cholesterol, LDL, and VLDL and elevates the reduction of HDL that was encouraged in Alloxan-induced diabetic rats. In the same way, the findings of red algae crude extract treatment attenuate the alterations of hypercholesterolemia and hyperlipidemia after induction of diabetes by Alloxan. This improvement in lipid profile may occur due to stimulating fatty acid biosynthesis and the incorporation of fatty acids into triglyceride in the liver and adipose tissue. The present study agrees with that of **Salib *et al.* (2013)** confirming that, T-Cholesterol, triglyceride, and LDL-cholesterol levels declined as a possible protection against hypercholesterolemia.

CONCLUSION

Based on the above findings, the current study highlighted the therapeutic potential of compounds of marine algae crude extract against diabetes and its complications. Furthermore, the present work paved the way for further research and potential development of seaweed green and green algae-based therapies for diabetic patients.

REFERENCES

Abo-Shady, A. M.; Gheda, S. F.; Ismail, G. A.; Cotas, J.; Pereira, L. and Abdel-Karim, O. H. (2023). Antioxidant and antidiabetic activity of algae. *Life.*, *13*(2): 460.

AbouGabal, A. A.; Khaled, A. A.; Aboul-Ela, H. M.; Aly, H. M.; Diab, M. H. and Shalaby, O. K. (2022). Marine Macroalgal Biodiversity, Spatial Study for the Egyptian Mediterranean Sea, Alexandria Coast. *Thalassa: An International Journal of Marine Sciences.*, *38*(1): 639-646.

Alam, M. A.; Parra-Saldivar, R.; Bilal, M.; Afroze, C. A.; Ahmed, M. N.; Iqbal, H. M. and Xu, J. (2021). Algae-derived bioactive molecules for the potential treatment of SARS-CoV-2. *Molecules*., *26*(8): 2134.

Bhandari, M. R.; Jong-Anurakkun, N.; Hong, G. and Kawabata, J. (2008). α-Glucosidase and α-amylase inhibitory activities of Nepalese medicinal herb Pakhanbhed (Bergenia ciliata, Haw) *Food Chemistry.*, *106*(1): 247-252.

Bürgi, W.; Briner, M.; Franken, N. and Kessler, A. C. (1988). One-step sandwich enzyme immunoassay for insulin using monoclonal antibodies. *Clinical Biochemistry*., *21*(5): 311-314.

Cardoso, S. M.; Pereira, O. R.; Seca, A. M.; Pinto, D. C. and Silva, A. M. (2015). Seaweeds as preventive agents for cardiovascular diseases: From nutrients to functional foods. *Marine Drugs*., *13*(11): 6838-6865.

Choudhary, B.; Chauhan, O. P. and Mishra, A. (2021). Edible seaweeds: a potential novel source of bioactive metabolites and nutraceuticals with human health benefits. *Frontiers in Marine Science*, *8*, 740054.

de Sousa, E.; Zanatta, L.; Seifriz, I.; Creczynski-Pasa, T. B.; Pizzolatti, M. G.; Szpoganicz, B. and Silva, F. R. M. B. (2004). Hypoglycemic Effect and Antioxidant Potential of Kaempferol-3, 7-O-(α)-dirhamnoside from Bauhinia f officiate Leaves. *Journal of natural products*., *67*(5): 829-832.

Dixit, Y. and Kar, A. (2010). Protective role of three vegetable peels in alloxan induced diabetes mellitus in male mice. *Plant Foods for Human Nutrition.*, *65*: 284-289.

Dods, R. F. (2003). Diabetes Mellitus Clinical Chemistry: Theory Analysis, Correlation. Kaplan, LA, Pesce. *AJ, and Kazmierczak, SC*, *580*.

Ebuehi, O. A. T.; Ajuluchukwu, A. E.; Afolabi, O. T. and Akinwande, A. I. (2010). Oxidative stress in alloxan-induced diabetes in female and male rats. *Adv. Med. Dent. Sci., 3*: 71-75.

El Gamal, A. A. (2010). Biological importance of marine algae. *Saudi pharmaceutical journal*., *18*(1): 1-25.

El-Sayed, A. E. K. B.; Fetyan, N. A.; Moghanm, F. S.; Elbagory, M.; Ibrahim, F. M.; Sadik, M. W. and Shokr, M. S. (2022). Biomass fatty acid profile and fuel property prediction of bagasse waste grown Nannochloropsis oculata. *Agriculture*., *12*(8): 1201.

Enzing, C.; Ploeg, M.; Barbosa, M. and Sijtsma, L. (2014). Microalgae-based products for the food and feed sector: an outlook for Europe. *JRC Scientific and policy reports*., 19-37.

Fossati, P. and Prencipe, L. (1982). Serum triglycerides are determined calorimetrically with an enzyme that produces hydrogen peroxide. *Clinical Chemistry*., 28: 2077-2080.

Furman, B. L. (2015). Streptozotocin-induced diabetic models in mice and rats. *Current protocols in pharmacology*., *70*(1): 5-47.

Ghasemi, A.; Tohidi, M.; Derakhshan, A.; Hasheminia, M.; Azizi, F. and Hadaegh, F. (2015). Cut-off points of homeostasis model assessment of insulin resistance, beta-cell function, and fasting serum insulin to identify future type 2 diabetes: Tehran Lipid and Glucose Study. *Acta diabetologica*, *52*: 905-915.

Goldner, M. G. and Gomori, G. (1944). Studies on the mechanism of alloxan diabetes. *Endocrinology*, *35*(4): 241-248.

Guiry, M. D. (2001). Macroalgae of Rhodophycota, Phaeophycota, Chlorophycota, and two genera of Xanthophycota, in: Costello, M.J. et al., (Ed.) (2001). European register of marine species: a check-list of the marine species in Europe and a bibliography of guides to their identification. Collection Patrimoines Naturels, 50: pp. 20-38.

Guiry, M. D. (2013). AlgaeBase. World-wide electronic publication. *http://www. algaebase. org*.

Hamden, K.; Allouche, N.; Damak, M. and Elfeki, A. (2009). Hypoglycemic and antioxidant effects of phenolic extracts and purified hydroxytyrosol from olive mill waste in vitro and in rats. *Chemico-biological interactions*, *180*(3): 421-432.

Hind, K. R. and Saunders, G. W. (2013). A molecular phylogenetic study of the tribe Corallineae (Corallinales, Rhodophyta) with an assessment of genus-level taxonomic features and descriptions of novel genera. *Journal of phycology*, *49*(1): 103-114.

Hussaini, S. M. A. K.; Hossain, M. I.; Islam, M. S. and Rafiq, K. (2018). Effects of Spirulina platensis on alloxan induced diabetic rats. *Progressive Agriculture*, *29*(2): 139-146.

Ibrahim, M. I.; Amer, M. S.; Ibrahim, H. A. and Zaghloul, E. H. (2022). Considerable production of ulvan from ulva lactuca with special emphasis on its antimicrobial and anti-fouling properties. *Applied Biochemistry and Biotechnology.*, *194*(7): 3097-3118.

Ikewuchi, J. C.; Onyeike, E. N.; Uwakwe, A. A. and Ikewuchi, C. C. (2011). Effect of aqueous extract of the leaves of Acalypha wilkesiana 'Godseffiana'Muell Arg (Euphorbiaceae) on the hematology, plasma biochemistry and ocular indices of oxidative stress in alloxan induced diabetic rats. *Journal of Ethnopharmacology*., *137*(3): 1415-1424.

Juárez-Reyes, K.; Brindis, F.; Medina-Campos, O. N.; Pedraza-Chaverri, J.; Bye, R.; Linares, E. and Mata, R. (2015). Hypoglycemic, antihyperglycemic, and antioxidant effects of the edible plant Anoda cristata. *Journal of ethnopharmacology.*, *161*: 36-45.

Judith S, and Main M. (1990). Procedures for Identifying infants as disorganized during the Anisworth Strange Situation. Attachment in preschool years: Theory, research, and Intervention, 1: 121-160.

Kalita, D.; Holm, D. G.; LaBarbera, D. V.; Petrash, J. M. and Jayanty, S. S. (2018). Inhibition of α-glucosidase, α-amylase, and aldose reductase by potato polyphenolic compounds. *PloS one*., *13*(1): 0191025.

Kim, S. K. and Chojnacka, K. editors. (2015). *Marine algae extracts: processes, products, and applications*. John Wiley and Sons.

KWON, Y. I.; Apostolidis, E. and Shetty, K. (2008). Inhibitory potential of wine and tea against α-amylase and α-glucosidase for management of hyperglycemia linked to type 2 diabetes. *Journal of Food Biochemistry*., *32*(1): 15-31.

Labbaci, F. Z. and Boukortt, F. O. (2020). Beneficial effects of Algerian green alga ulva lactuca and its hydroethanolic extract on insulin resistance and cholesterol reverse transport in high-fat/streptozotocin diabetic rats. *Preventive Nutrition and Food Science*., *25*(4): 353.

Lalegerie, F.; Lajili, S.; Bedoux, G.; Taupin, L.; Stiger-Pouvreau, V. and Connan, S. (2019). Photo-protective compounds in red macroalgae from Brittany: Considerable diversity in mycosporine-like amino acids (MAAs). *Marine environmental research*., *147*, 37-48.

Lee, C. W. and Han, J. S. (2012). Hypoglycemic effect of Sargassum ringgoldianum extract in STZ-induced diabetic mice. *Preventive nutrition and food science*., *17*(1): 8.

Lee, M. Y.; Choi, D. S.; Lee, M. K.; Lee, H. W.; Park, T. S.; Kim, D. M. and Shin, H. K. (2014). Comparison of acarbose and voglibose in diabetes patients who are inadequately controlled with basal insulin treatment: randomized, parallel, open-label, active-controlled study. *Journal of Korean medical science.*, *29*(1): 90-97.

Li, S.; Chen, H.; Wang, J.; Wang, X.; Hu, B. and Lv, F. (2015). Involvement of the PI3K/Akt signal pathway in the hypoglycemic effects of tea polysaccharides on diabetic mice. *International Journal of Biological Macromolecules*., *81*: 967-974.

Marchini, A.; Ragazzola, F.; Vasapollo, C.; Castelli, A. ;Cerrati, G.; Gazzola, F. and Lombardi, C. (2019). Intertidal Mediterranean coralline algae habitat is expecting a shift toward a reduced growth and a simplified associated fauna under climate change. *Frontiers in marine Science*., *6*: 106.

Muniyappa, R.; Lee, S.; Chen, H. and Quon, M. J. (2008). Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *American Journal of Physiology-Endocrinology and Metabolism*., *294*(1): E15-E26.

Paul, J. P. J. and Yuvaraj, P. (2013). Phytochemical analysis of Padina distromatica Hauck. *Indo American Journal of Pharmaceutical Research.*, *3*(7): 5290-5297.

Ruiz, J.; Olivieri, G.; De Vree, J.; Bosma, R.; Willems, P.; Reith, J. H. and Barbosa, M. J. (2016). Towards industrial products from microalgae. *Energy and Environmental Science*., *9*(10): 3036-3043.

Ścieszka, S. and Klewicka, E. (2019). Algae in food: A general review. *Critical reviews in food science and nutrition*., *59*(21): 3538-3547.

Shahidi, F. and Rahman, M. J. (2018). Bioactives in seaweeds, algae, and fungi and their role in health promotion. *Journal of Food Bioactives*., *2*: 58-81.

Shirwaikar, A.; Rajendran, K.; Kumar, C. D. and Bodla, R. (2004). Antidiabetic activity of aqueous leaf extract of Annona squamosa in streptozotocin–nicotinamide type 2 diabetic rats. *Journal of ethnopharmacology*., *91*(1): 171-175.

Srinivasan, K. and Ramarao, P. (2007). Animal models in type 2 diabetes research: an overview. *Indian journal of medical research*., *125*(3): 451-472.

Szkudelski, T. (2001). The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiological research.*, *50*(6): 537-546.

Tiwari, B. K. and Troy, D. J. (2015). Seaweed sustainability–food and nonfood applications. In *Seaweed sustainability*: 1-6. Academic Press.

Valado, A.; Pereira, M.; Amaral, M.; Cotas, J. and Pereira, L. (2022). Bioactivity of carrageenans in metabolic syndrome and cardiovascular diseases. *Nutraceuticals*., *2*(4): 441-454.

Vasudevan, D. M.; Sreekumari, S. and Vaidyanathan, K. (2013). *Textbook of biochemistry for medical students*. JP Medical Ltd.

Warnick, G. R. and Wood, P. D. (1995). National cholesterol education program recommendations for measurement of high-density lipoprotein cholesterol: Executive summary. The national cholesterol education program working group on lipoprotein measurement. *Clinical chemistry.*, *41*(10): 1427-1433.

Yang, Y.; Liu, D.; Wu, J.; Chen, Y. and Wang, S. (2011). In vitro antioxidant activities of sulfated polysaccharide fractions extracted from Corallina officinalis. *International Journal of Biological Macromolecules.*, *49*(5), 1031-1037.

Yin, P.; Zhao, S.; Chen, S.; Liu, J.; Shi, L.; Wang, X. and Ma, C. (2011). Hypoglycemic and hypolipidemic effects of polyphenols from burs of Castanea mollissima Blume. *Molecules.*, *16*(11): 9764-9774.

Zaatout, H.; Ghareeb, D.; Abd-Elgwad, A. and Ismael, A. (2019). Phytochemical, antioxidant, and anti-inflammatory screening of the Egyptian Ulva lactuca methanolic extract. *Records of Pharmaceutical and Biomedical Sciences.*, *3*(2): 33-38.