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EVALUATION OF ANTIDIABETIC EFFICACY OF BROWN ALGA *SPATOGLOSSUM ASPERUM* J. AGARDH BY ALLOXAN STIMULATED HYPERGLYCEMIA ON WISTAR ALBINO RATS

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ABSTRACT: The present investigation aims to evaluate the effect of methanol extract of *Spatoglossum asperum* for its anti-hyperglycemic activity against diabetics induced by alloxan in Wistar albino rats. Artificially diabetes was induced in albino rats by the administration through injection of a single dose of alloxan monohydrate (10 mg/kg, I.P). The 10 mg/kg methanol residue of *S. asperum* was administered as a single oral dose per day to diabetes-induced rats for 28 days. The outcome of algae residue feeding was estimated by various biochemical and hematological parameters such as RBC, WBC, Hb, and platelets and lipid profile. After feeding of algal methanol extract of *S. asperum* in diabetic rats for 28 days, the blood glucose had significantly decreased, whereas the liver glycogen level had increased. Histopathological examination of the pancreas was done. The methanol residues of the *Spatoglossum asperum* possess very effective anti-hyperglycemic activity on the diabetic rats as compared to glipizide.

INTRODUCTION: Diabetes mellitus is a common disease affecting the citizens of both developed and developing countries. India is one of the leading countries for the number of people with diabetes mellitus, and it is estimated that diabetes would affect approximately 57 million people by the year 2025 in India. The main reasons of morbidity and mortality in the diabetic patients are cardiovascular diseases as patients are 2 to 4 times more susceptible to have heart disease and 5 times more likely to have a stroke^{1,2}.

The control and treatment of diabetes and its complications mainly depend on the chemical and biochemical agents. Recently, the medicinal values of various plant extracts have been studied by many scientists in the field of diabetic research, and they contain valuable medicinal properties in different parts of the plant, and the major merits of herbal medicines seem to be their efficacy, low incidence of side-effects and low cost^{3,4}.

Algae are a great source of natural compounds which are widely known and consumed in Asian countries⁵. Seaweeds are considered as a source of bioactive compounds as they can produce a great variety of secondary metabolites characterized by a broad spectrum of biological activities, especially anti-diabetic activities^{6,7,8,9,10}. In this study, we attempted the anti-hyperglycemic effect of methanol extract of brown alga *Spatoglossum*

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asperum J. Agardhon alloxan stimulated hyperglycemic Wistar albino rats.

MATERIALS AND METHODS:

Collection of Marine Alga *Spatoglossum asperum*: Fresh materials of *Spatoglossum asperum* were obtained from Mandapam, the South East coast of Tamil Nadu and the algae were identified by the standard manual¹¹. The voucher specimen (PCCACL08) was deposited as Herbarium in the Department of Botany, Pachaiyappa's College and Chennai- 600030. The salt and sand stuck on the surface of the freshly collected samples were removed by using sterilized seawater.

Extraction of Marine Alga: The shade dried seaweeds were finely powdered using a blender and stirred in with methanol in Soxhlet apparatus. The extract was evaporated to dryness under vacuum and dried in a vacuum desiccator. The crude methanol algal extract was stored at room temperature for further analysis^{12, 13}.

Selection and Acclimatization of Animals: The Wistar strain of male albino rats weighing between 180-220 g were used for this study. The animals were housed in large spacious cages and fed with commercial pellets and access to water *ad libitum*. The animals were well acclimatized to the standard environmental condition of temperature (25 ± 2 °C) and humidity ($55 \pm 5\%$) and 12 h light/dark cycles throughout the experimental period^{12, 13}.

Acute Oral Toxicity Study: In order to assess the toxic effects and tolerance limit and to determine a safe dose an acute oral toxicity study was carried out as per the CPCSEA guidelines. The rats fasted for 3-4 h before administration of extracts. All procedures described were reviewed and approved by the Institute Animal Ethical Committee (IAEC) no: IAEC/KMCP/153/FT/ 9599/2013-2014.

Induction of Diabetes Mellitus: Diabetes mellitus was induced in male albino Wistar rats by a single intraperitoneal injection of a freshly prepared solution of alloxan monohydrate (10 mg/kg body weight) in physiological saline after overnight fasting for 12 h^{12, 13}. The development of hyperglycemia in rats was confirmed by plasma glucose estimation 72 h post alloxan injection. The rats with fasting plasma glucose level of 160-220 mg/dL were used for this experiment.

Experimental Procedure: In the experiment, a total of 24 rats (18 diabetic surviving rats and 6 normal rats), each group with 6 rats was used. Diabetes was induced in rats 3 days before starting the experiment. The rats were divided into 4 groups after the induction of alloxan diabetes^{12, 13}.

Treatment Protocol: The experimental rats were divided into 4 groups of six rats as follows:

Group I: Normal control rats, received 0.9% saline at a dose of 10 mL/kg/body weight/rat/day for 28 days.

Group II: Alloxan induced diabetic rats, received 10 mg/kg body weight/rat/day of alloxan monohydrate through Intraperitoneal injection for 28 days.

Group III: Diabetic rats treated with glipizide (5 mg/kg/body weight/rat/day) dissolved in aqueous solution orally for 28 days¹⁴.

Group IV: Diabetic rats, treated with methanol extract residue of *S. asperum* (10 mg/kg/body weight/rat/day) dissolved in aqueous solution orally for 28 days.

Histo-Chemical Parameters: After 28 days of treatment, the blood glucose level and the bodyweight of the experimental rats were measured. Then blood was collected retro-orbitally under mild ether anesthesia using capillary tubes. Blood was collected from the eyes (venous pool) by a sino-ocular puncture in fresh vials containing EDTA as anticoagulant agents and plasma were separated in a T8 electric centrifuge at 3000 rpm for 4 min. Then the animals were sacrificed by euthanasia. Liver and pancreas were immediately dissected out, washed in ice-cold saline to remove the blood and liver was used for estimation of enzyme activity while pancreas was subjected to histopathological studies. Blood, as well as tissue samples, were collected for the assessment of plasma glucose, hepatic glucokinase, hexokinase, glucose 6-phosphate, and phosphofructokinase content along with glycogen content.

Biochemical Analysis: Plasma insulin was determined by the ELISA method using a Boehringer-Mannheim kit with an ES300 Boehringer analyzer (Mannheim, Germany)¹⁴. Hemoglobin was estimated by the method of

Drabkin and Austin (1932)¹⁵. Glycosylated hemoglobin (HbA1C) was estimated by following the method of Hongayo (2011). Hepatic glucokinase and hexokinase activity was assayed by means of glucose 6 phosphate-dependent spectrophotometric method Hongayo (2011). The glucose-6-phosphatase activity was estimated by calorimetrically Hongayo (2011). Glycogen content was determined colorimetrically by the method of Hongayo¹⁶.

Parameters: Blood samples were assessed for RBC, WBC, HB, and platelets with an auto-analyzer (MISPA-EXCEL, Japan).

Estimation of Lipid Profile: Total serum cholesterol in the blood was estimated by using reported method¹⁷. Estimation of HDL-C and LDL-C [Zawistowski, 2009] was done based on the following principle:

Phosphotungstate / Mg²⁺ precipitates chylomicrons, LDL and VLDL fractions. High-density lipoprotein (HDL) fraction remains unaffected in the supernatant. Cholesterol content of HDL fraction was assayed using Autozyme cholesterol. The total phospholipids in the serum were estimated by the method of the Post and Sen (1967)¹⁷. Determination of triglycerides was done based on the principle that glycerol released from hydrolysis of triglycerides by lipoprotein lipase is converted by glycerol kinase into glycerol - 3 - phosphate, which is oxidized by glycerol phosphate oxidase to dihydroxyacetone phosphate and hydrogen peroxide. In the presence of peroxidase, hydrogen peroxide oxidizes phenolic chromogen to a red colored compound.

TABLE 1: EFFICIENCY OF THE METHANOL EXTRACT RESIDUE OF *S. ASPERUM* ON BODY WEIGHT OF NORMAL AND EXPERIMENTAL ANIMALS

Groups	Initial body weight (g)	Final body weight (g)
Normal control - (Group I)	227.50 ± 4.50	231.30 ± 5.80
Toxic control - Alloxan monohydrate (Group II)	198.60 ± 2.80	156.40 ± 4.20 ^(*a)
Positive control - Diabetic + Glipizide (Group III)	213.50 ± 2.50	215.30 ± 4.40 ^(*b)
Treatment control – Diabetic + Methanol extract of <i>S. asperum</i> (Group IV)	226.35 ± 3.95	231.56 ± 3.68 ^(*b)

Effect of Methanol Extract of *S. asperum* on Blood Glucose Levels: Before Alloxan administration, the basal level of plasma glucose of the rats were not significantly higher in the rats selected for the study. In contrast, non-diabetic control (Group I) remained steadily euglycemic throughout the study. Alloxan induced diabetic

Histopathological Examination of Pancreas: The pancreas tissue section was fixed in 4 g/L formaldehyde and embedded in paraffin. Paraffin section was then stained with hematoxylin-eosin¹⁷. Each sample was observed at 400 X magnification and scored according to the injuries.

Statistical Analysis: All the experimental values in this investigation were expressed as mean ± SD. All pair-wise multiple comparison procedures were attempted by Student-Newman-Keuls procedure using One-way ANOVA followed by SPSS 17.0. P<0.01 was considered to be significant. Triplicate assays were performed for each set of test conditions.

RESULTS: The *in-vivo* anti-diabetic activity of the methanol extract of marine brown alga *S. asperum* alloxan-induced diabetes showed significant results.

Effect of Methanol Extract of *S. asperum* Body Weight of Normal and Experimental Animals: Table 1 illustrates the bodyweight of the Group I to IV. The mean body weight of diabetic rats is 198.60 ± 2.80g which had significantly decreased to 156.40 ± 4.20 g, as compared to normal animal body weight (231.30 ± 5.80 g). The positive control, *i.e.* drug (Glipizide 5 mg/kg body weight) treated animals showed a recovery from bodyweight loss.

Treatment with methanol extract of *S. asperum* at a dose of 10 mg/kg body weight, exhibited an excellent recovery to keep the bodyweight comparable to that of normal control animals (Group I).

animals (Group II) recorded more than twofold higher glucose (230.10 ± 5.70 mg/dL) as compared to that of normal animals (92.00 ± 2.30 mg/dL). At the end of the experiment, the diabetic induced animals had 138.1% of glucose than normal animals. Both the group III and IV, levels of glucose were restored to normal Table 2.

The methanol extract of *S. asperum* treated group IV (10 mg/kg body weight), showed a significant anti-hyperglycemic ($P < 0.001$) effect at the end of the 14th day; the decrease in blood sugar was

maximum on completion of the 28th day. Similarly, in group III animals, it also restored the blood sugar level nearly to that of the normal range.

TABLE 2: EFFICIENCY OF 4 WEEKS TREATMENT WITH METHANOL EXTRACT RESIDUE OF *S. ASPERUM* ON GLUCOSE LEVELS IN ALLOXAN DIABETIC RATS

Groups	0 Day	14 th Day	28 th Day
Normal control - (Group I)	88.20 ± 5.20	93.50 ± 4.80	92.00 ± 2.30
Toxic control - Alloxon monohydrate (Group II)	160.20 ± 5.20	188.30 ± 4.70 ^(*a)	230.10 ± 5.70 ^(*a)
Positive control - Diabetic+Glipizide (Group III)	184.50 ± 4.20	154.80 ± 3.80 ^(*b)	140.50 ± 2.30 ^(*b)
Treatment control - Diabetic+Methanol extract of <i>S. asperum</i> (Group IV)	194.36 ± 4.23	162.30 ± 3.75 ^(*b)	153.85 ± 2.55 ^(*b)

Unit: mg, No. of animals in each group (n) = 6, Values are expressed as Mean ± SEM. Values were found out by using One Way ANOVA followed by Newman Keul's multiple range tests. ^(*a) Values were significantly different from normal control (G_I) at $P < 0.001$. ^(*b) Values were significantly different from diabetic control (G_{II}) at $P < 0.001$.

Effect of Methanol Extract on Glycogen Content:

Glycogen content of liver tissue estimated on the 28th day in all the four groups of experimental animals **Table 3** showed that in Group II, the liver glycogen content decreased significantly by 33.60% as compared to non-diabetic control animals. Whereas in group III and IV the liver glycogen level increased by 21.90 and 21.06% respectively.

TABLE 3: EFFICIENCY OF ADMINISTRATION OF METHANOL EXTRACT RESIDUE OF *S. ASPERUM* ON GLYCOGEN CONTENT OF LIVER TISSUE OF RATS

Groups	Liver tissue glycogen content (mg/g)
Normal control - (Group I)	48.20 ± 2.80
Toxic control - Alloxan monohydrate (Group II)	14.60 ± 2.50 ^(*a)
Positive control - Diabetic + Glipizide (Group III)	36.50 ± 5.20 ^(*b)
Treatment control - Diabetic + extract of <i>S. asperum</i> (Group IV)	35.66 ± 1.34 ^(*b)

Effect of Methanol Extract on Hepatic Enzymes:

To establish the diabetic condition, plasma glucose and glycogen content were determined 72 h after alloxan administration and the hepatic enzymes hexokinase, glucokinase and glucose-6-phosphate were estimated in all the groups (I to IV), 28 days after induction of diabetes **Table 4**. Non-diabetic control animals recorded notable values for enzyme hexokinase (0.252 ± 0.01), glucose-6-phosphate (0.143 ± 0.00) and glucokinase (30.50 ± 0.60).

Diabetic induced animals showed reduced levels of the enzymes hexokinase, glucose-6-phosphate, and glucokinase in their liver tissue as 0.100 ± 0.08, 0.146 ± 0.01 and 6.24 ± 0.11 respectively when compared to non-diabetic control. In group III and IV, the values are increased with respect to all the parameters. The observed levels between these two groups of animals were comparable with each other **Table 4**. However, they could not be restored to the levels observed in non-diabetic controls.

TABLE 4: EFFICIENCY OF ADMINISTRATION OF THE METHANOL EXTRACT RESIDUE OF *S. ASPERUM* ON HEPATIC ENZYMES INVOLVED IN CARBOHYDRATE METABOLISM IN RATS

Groups	Hexokinase	Glucose 6-Phosphate	Glucokinase
Normal control - (Group I)	0.252 ± 0.01	0.143 ± 0.00	30.50 ± 0.60
Toxic control - Alloxan monohydrate (Group II)	0.100 ± 0.08 ^(*a)	0.146 ± 0.01 ^(*a)	6.24 ± 0.11 ^(*a)
Positive control - Diabetic + Glipizide (Group III)	0.167 ± 0.00 ^(*b)	0.330 ± 0.00 ^(*b)	21.24 ± 0.43 ^(*b)
Treatment control - Diabetic + Extract of <i>S. asperum</i> (Group IV)	0.153 ± 0.00 ^(*b)	0.297 ± 0.00 ^(*b)	17.30 ± 0.38 ^(*b)

Unit = one unit is as 50% inhibition of NBT/mg protein. Unit = μmoles of H₂O₂ utilized/min/mg protein. Unit = μg/100 mg tissue. N = 6 in each group, values are expressed as Mean ± SEM. Values were found out by using One Way ANOVA followed by Newman Keul's multiple range tests. ^(*a) Values were significantly different from normal control (G_I) at $P < 0.001$. ^(*b) Values were significantly different from diabetic control (G_{II}) at $P < 0.001$. Values with different superscripts in the same row differ significantly at 5% level $P < 0.05$.

Effect of Methanol Extract of *S. asperum* on Haematological Parameters:

The effect of methanol extract residue on parameters in diabetic induced rats (Group II) are shown in **Table 5**. At the end of the study period, there was a significant reduction of white blood corpuscles (9.10 ± 0.40

10³ μL), red blood corpuscles (5.20 ± 0.14 10⁶ μL), platelet counts (315.40 ± 20.14 10³ μL) and slightly an increase in the haemoglobin (13.24 ± 0.60 gm/dL) level of the diabetic induced rats, compared to that of non-diabetic animals (Group I). No significant differences were seen in the mean value

of WBC, RBC, HB and platelet counts in the positive control (Group III) and in the treatment control (Group IV) as compared to the non-diabetic animals.

TABLE 5: EFFICIENCY OF ADMINISTRATION OF THE METHANOL EXTRACT RESIDUE OF *S. ASPERUM* ON HAEMATOLOGICAL PARAMETERS

Groups	WBC	RBC	HB	Platelets
Normal control - (Group I)	9.50 ± 0.60	5.30 ± 0.40	10.52 ± 0.46	312.20 ± 35.00
Toxic control - Alloxan monohydrate (Group II)	9.10 ± 0.40	5.20 ± 0.14	13.24 ± 0.60	315.40 ± 20.14
Positive control - Diabetic + Glipizide (Group III)	8.20 ± 0.40	5.20 ± 0.20	14.02 ± 0.40	291.40 ± 20.00
Treatment control - Diabetic + Extract of <i>S. asperum</i> (Group IV)	9.05 ± 0.70	5.15 ± 0.32	11.78 ± 0.32	292.25 ± 26.35

Unit: For WBC -10³/μL, RBC-10⁶/μL, HB-gm/dL, Platelet-10³/mL

Effect of Methanol Extract of *S. asperum* on Lipid Profile: The lipid profile Table 6 showed a significant increase in total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein (LDL) and phospholipids level, with a decrease in HDL level in alloxan-induced diabetic rats as compared to normal rats. Treatment of normal and alloxan-induced diabetic rats with the methanol extract residue of *S. asperum* at a dose of

10 mg/kg weight for 28 days resulted in a marked decrease in total cholesterol (117.50 ± 3.33 mg/dL), triglycerides (97.22 ± 2.55 mg/dL), low density lipoprotein (24.40 ± 1.75 mg/dL) and phospholipids level (155.25 ± 3.92 mg/dL) and increase in HDL (41.50 ± 1.61 mg/dL) levels as compared to alloxan-induced diabetic rats that were equal to the positive control (Group III).

TABLE 6: EFFICIENCY OF ADMINISTRATION OF THE METHANOL EXTRACT RESIDUE OF *S. ASPERUM* ON CHOLESTEROL, TRIGLYCERIDE, HDL-C, LDL-C AND PHOSPHOLIPIDS

Groups	Total Cholesterol (mg/dL)	Triglyceride (mg/dL)	High density lipoprotein (HDL-C) (mg/dL)	Low density lipoprotein (LDL) (mg/dL)	Phospholipids (mg/dL)
Normal control - (Group I)	83.20 ± 2.53	86.20 ± 1.75	48.92 ± 2.70	15.20 ± 3.20	122.50 ± 2.10
Toxic control - Alloxan monohydrate (Group II)	229.50 ± 5.00 ^(**a)	157.10 ± 6.25 ^(**a)	29.80 ± 2.20 ^(**a)	36.89 ± 3.50 ^(**a)	203.70 ± 5.80 ^(**a)
Positive control - Diabetic + Glipizide (Group III)	103.90 ± 2.50 ^(**b)	92.50 ± 3.25 ^(**b)	42.90 ± 3.45 ^(**b)	21.20 ± 2.80 ^(**b)	146.80 ± 4.50 ^(**b)
Treatment control - Diabetic + Extract of <i>S. asperum</i> (Group IV)	117.50 ± 3.33 ^(**b)	97.22 ± 2.55 ^(**b)	41.50 ± 1.61 ^(**b)	24.40 ± 1.75 ^(**b)	155.25 ± 3.92 ^(**b)

Values are expressed as mean ± SEM. Values were compared by using analysis of variance (ANOVA) followed by Newman-Keul's multiple range tests. ^(**a) Values are significantly different from toxic control G_{II} at P<0.01. ^(**b) Values are significantly different from toxic control G_{II} at P<0.01.

Histopathological Study: Histopathological observation Fig. 1a showed the normal acini and normal cellular population in the islets of Langerhans in the pancreas of normal rats (Group I). Extensive damage of islets of Langerhans in the pancreas of diabetic rats (Group II) and their reduction was observed Fig. 1b. The presence of lymphocytic infiltrates in the islet of Langerhans is characteristic of certain types of autoimmune disease.

The diabetic mice treated with glipizide showed restoration of the normal cellular population size of Islets with hyperplasia (Group III) Fig. 1c. Most of the nuclei were darkly stained than the surrounding acinar cells. The partial restoration of normal cellular population and enlarged size of β-cells with hyperplasia (Group IV) were observed Fig. 1d.

DISCUSSION: The present study was carried out to assess the anti-hyperglycemic property of the methanol extract of *S. asperum* in the control of diabetes on Wistar albino rats. Experimentally induced diabetes was used to analyze the biochemical, hormonal and morphological parameters during severe insulin deficiency or even during death.

In the present study, diabetes mellitus was induced by alloxan monohydrate at a dose of 10 mg/kg body weight. A significant increase in the plasma insulin level was observed when diabetic rats were treated with the methanol extract of *S. asperum* at a dose of 10 mg/kg body weight. In the case of uncontrolled diabetes rats, there is an increased number of proteins including hemoglobin and α-crystalline of the lens¹⁸. Glycosylated hemoglobin

(HbA_{1c}) was found to increase in patients with diabetes mellitus to approximately 16%.¹⁶ During diabetes, the excess glucose present in the blood reacts with hemoglobin. Therefore, the total level decreases in alloxan-induced diabetic rats^{14, 16}. Administration of the methanol extract of *S. asperum* at a dose of 10 mg/kg bodyweight for 28 days prevents a significant elevation in glycosylated, thereby increasing the level of total in diabetic rats. This could be due to the result of

improved glycaemic control produced by the extract of *S. asperum*. In the diabetes mellitus affected rats, proteins are used as an energy source; this leads to a decrease in protein storage, which in turn reduces the bodyweight¹⁶. The decrease in body weight was observed in alloxan-induced diabetic rats¹⁴. The administration of methanol extract of *S. asperum* at a concentration of 10 mg/kg body weight, led to an increase in the body weight in diabetic rats.

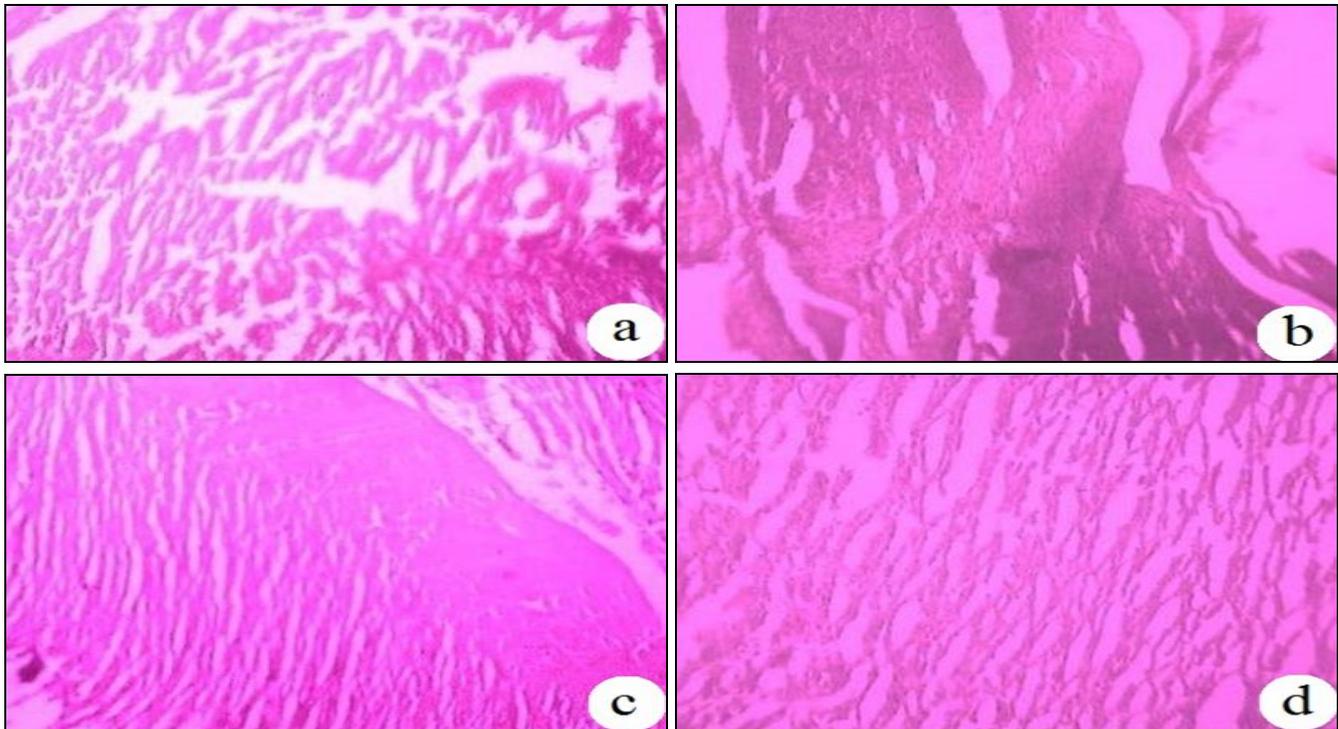


FIG. 1: PHOTOMICROGRAPH OF A CROSS-SECTION OF PANCREAS STAINED WITH HAEMATOXYLIN AND EOSIN (MAGNIFICATION $\times 400X$). a) Normal Control (Group I); b) Toxic Control (Alloxan monohydrate) (Group II); c) Positive Control (Alloxan monohydrate + Glipizide) (Group III); d) Treatment group (Alloxan monohydrate + extract of *S. asperum*) (Group IV)

In the alloxan-induced diabetes mellitus rats, the rise in blood glucose was accompanied by an increase in serum cholesterol and triglycerides. The levels of cholesterol, triglycerides, and low-density lipoprotein (LDL) levels seemed to be nearly normal when treated with the methanol extract of *S. asperum* at a dose of 10 mg/kg body weight in the diabetic rats. Normalization of increased blood glucose by *S. asperum* extract suggests that it may enhance glucose transport across the cell membranes and stimulate glycogen synthesis or enhance glycolysis. Similarly, anti-hyperglycemic effects have been observed by the restoration of blood glucose level to normal in diabetic rats through different solvent extracts of brown alga *Cystoseira moniliformis*,¹⁶ *Padina arborescens*¹⁹ and *Lobophora variegata*¹³.

There was an improvement in *S. asperum* extract and glipizide treated rats on liver protein levels, which might be due to the marked changes in circulating amino acid level, hepatic amino acid uptake and muscle output of amino acid concentrations¹⁹. The increased hepatic glucose output in diabetes may be derived from gluconeogenesis^{20, 21}. The effect of methanol extract of *S. asperum* at a dose of 10 mg/kg on diabetic hypertriglyceridemia could be through its control of hyperglycemia. The improved glycaemic control following sulfonylurea therapy decreases the levels of serum VLDL and total triglycerides²².

The reduction in serum total cholesterol levels and dietary cholesterol absorption in the treated groups (fed with the algal extracts and drug) relative to the

hypercholesterolemic control group was a likely explanation for the observed reduction in LDL-C levels²². The elevated level of LDL-C got significantly reduced in the algal treated rats, which may be due to the antioxidant property of the extracts, which are capable of inhibiting the LDL-C peroxidation²³. The HDL-C is a free radical scavenger and prevents peroxidation of beta lipoproteins²⁴. Rats treated with algal extracts showed improved high levels of HDL-C, which may be due to the ability of the extract to accelerate the decomposition of free radical species generated during cholesterol administration^{25, 26}. The liver enzymes are normally found in circulation in small amounts because of the hepatic growth and repair. ALT, AST and ALP activities were elevated in hypercholesterolemic groups, meanwhile, the treated groups (IV) showed an obvious enhancement. The antihypercholesterolemic activity was due to the reduced cholesterol absorption in the gut¹⁷.

The result of the present study clearly showed that the level of HDL-C was increased in alloxan-induced diabetic rats when treated with methanol extract residue of *S. asperum* at a dose of 10 mg/kg. These results confirm the reduction of intestinal glucose transport *in-vivo* and may be due to increased insulin sensitivity as observed in previous studies²⁷. Hexokinase is the prime enzyme catalyzing glucose phosphorylation²⁸. In the present study, hexokinase activity was found to be decreased in diabetic rats which may be due to insulin deficiency. Treatment with *S. asperum* elevated the activity of the hexokinase in liver and kidney. The *S. asperum* may stimulate insulin secretion, which in turn activates hexokinase, thereby increasing the utilization of glucose leading to decreased blood sugar levels. Seaweeds contain numerous bioactive substances that have been shown to lower cholesterol and blood pressure and promote healthy digestion and antioxidant activity¹⁵. The presence of the bioactive metabolites in the marine brown alga *S. asperum* may explain the normalization of the FBS (Fasting blood sugar) level in diabetic rats. Dietary fucoxanthin also significantly reduced hepatic liver lipids and decrease in the lipid substrates for oxidation could result in the lower lipid hydroperoxide levels of the liver⁸. The biochemical and parameters of Wistar albino rats after feeding with the methanol extract

of *S. asperum* clearly indicated that it had not brought about any toxic impact on the rats. This was further confirmed by the quantification of total RBC, WBC and hemoglobin contents.

CONCLUSION: In the present study, the methanol extract of *S. asperum* at a dose of (10 mg/kg body weight) exhibited significant anti-hyperglycemic activity in alloxan-induced diabetic rats (Group IV). The extract showed improvement in the parameters like body weight, liver glycogen content and carbohydrate metabolizing enzymes as well as regeneration of β -cells of the pancreas in diabetes treatment. However, further pharmacological and biochemical investigations would elucidate the mechanism of action. The level of liver marker enzymes was also increased. The restoration of transaminases to their normal levels after the treatment also indicated a revival of insulin secretion. Histopathological examination reinforces the healing of the pancreas, by *S. asperum* methanol extracts, as a possible mechanism of their anti-diabetic activity.

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AUTHORS' CONTRIBUTION: All authors have contributed to the completion of this research work.

CONFLICT OF INTEREST: Authors have none to declare.

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