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# POTENT ANTIDIABETIC ACTIVITY OF AQUEOUS EXTRACT OF BROWN SEAWEED *PADINA BOERGESENII* IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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## ABSTRACT

Identification of new drugs from marine has major focus of researchers. In the present study, the effect of aqueous extract of brown algae *Padina boergesenii* in streptozotocin (STZ) induced diabetic rats. Diabetes mellitus was induced by a single intraperitoneal injection of STZ (60 mg/kg bw). Oral administration of the effective dose of *P. boergesenii* to the diabetic rats for 20 days showed abridged effects on protein, hemoglobin and glycosylated hemoglobin levels. Significant difference was observed serum urea, uric acid and creatinine levels in diabetic rats after *P. boergesenii* extract treatment ($p<0.005$). The extract of *P. boergesenii* significantly increased the activities of protein, hemoglobin in liver and kidney of control and experimental rats. The effect of urea, uric acid and creatinine was more pronounced in serum, liver and kidney lipid profile treatment with the *P. boergesenii* extract. The present study clearly indicated significant antidiabetic effect with the *P. boergesenii* shows to have a potential value for the development of an effective phytomedicine for diabetes and lends support for its traditional usage.

**KEYWORDS:** Seaweed, aqueous extract, *Padina boergesenii*, antidiabetic activity, Streptozotocin.

## INTRODUCTION

Type 2 diabetes is a clinically and heritably heterogeneous metabolic disorder expressed through unusually high levels of glucose in the blood.[1] It is a severe communal health problem, all over the humanity, with a predictable worldwide occurrence of 422 million people in 2014, compared to 108 million in 1980.The prevalence of diabetes has closely doubled since 1980, rising from 4.7% to 8.5% in the adult population.[2] It is boosting the search for novel methods and targets for the treatment of this incurable disease. The researchers are developing indigenous natural resources in order to for controlling diabetes.[3] The use of natural medicines for treatment of diabetes has been attempted for their antidiabetic potential by the various examinations in experimental animals.[4] In this present investigation is undertaken to explore the antidiabetic potential of a marine algae, *P. boergesenii* in type 2 diabetic animals.

In our earlier reports, *P. boergesenii* Allender & Kraft (Dictyotaceae), brown seaweed lavishly growing in Gulf of Mannar, Southeast coast of Tamilnadu, India was found to have on blood glucose, insulin, carbohydrate metabolism such as hexokinase, glucose-6-phosphatase and fructose- 1, 6-diphosphatase and lipid profile in STZ-induced diabetic rats.[5] Antioxidant effect.[6] Recently we have reported on the synthesis and characterization and antifungal activity of silver nanoparticles synthesized from *P. boergesenii*.[7] And potent α-glucosidase inhibitory activity of green synthesized gold nanoparticles[8] and it has also been reported for hepatoprotective activity.[9] Chemo preventive affects[10] and herbivory effects.[11]

Except the initial report, there is no report of systematic investigation of antidiabetic activity of aqueous extract of *P. boergesenii* STZ-induced diabetic rats. Thus, the aim of the present study was to perform detailed studies on the antidiabetic activity of aqueous extract of *P. boergesenii.*

## MATERIALS AND METHODS

### Drugs and chemicals

Streptozotocin (STZ) was purchased from Sigma–Aldrich Co, USA. All the biochemical used in this experiment were obtained from Sigma Chemical Company (St. Louis MO, USA). All other chemicals utilized were obtained either from Hi Media (Mumbai) or SD-Fine Chemicals (Mumbai). Reagents and chemicals used in the present study were of analytical grade.

**Animals and diet**

Adult wistar (albino) rats weighed between 150 to 200 g were obtained from animal house of Kongunadu arts and science college, Coimbatore, India. The animal tests were carried out according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The Institutional AnimalEthical Committee approved added experimental design performed in this study for the use of wistar albino rats as an animal model for antidiabetic activity. The animals were fed with standard pellet diet (Hindustan Lever Limited, Mumbai, India) and water freely available throughout the experimental period and replenished daily. The animals were housed in well ventilated large polypropylene cages under controlled conditions of light (12 hr light/12 hr dark), humidity (50-55 %) and ambient temperature (25 ± 2°C).

**Seaweed material**

*Padina boergesenii* (Allender & Kraft) was collected from Mandapam coastal region (78°8'E, 9°17'N), in Gulf of Mannar, Tamilnadu, South India on low tide during October 2015, The seaweed material was taxonomically identifiedand authenticated by the Botanical Survey of India and the voucherspecimen (No.BSI/SRC/5/23//TECH486) was retained in our laboratory for future reference.

**Preparation of seaweed extract**

The collected algae were instantlytransported to the laboratory in polythene bags with seawater and washed numerous times with seawater to remove sand, mud and attached fauna. The seaweedwas cleaned using brush for the removal of epiphytes with distilled water. After cleaning, seaweedwas dried in shade at room temperature for one week. The dried seaweedmaterials were homogenized to fine powder and further subjected to extraction. About 50 g of powdered seaweed material was mixed with 250 ml of double distilled water in a 500 ml conical flask and was placed in shaker for 16 h. The solution was then extracted using a separating funnel and was concentrated by lyophilizer. A brownish-black powdered material was obtained (12 g) and stored in a dessicator and used for further experiments. The pH was adjusted to 7.5-8 and osmolarity was adjusted to 290-300 mOsm respectively.

**Induction of experimental diabetes**

Type 2diabetes was induced by single intraperitoneal injection of 60 mg/kg of Streptozotocin (STZ) freshly dissolved in cold citrate buffer, pH 4.5.[12] Control animals received only citrate buffer. After two weeks rats with moderate diabetes having glycosuria, indicated by

Benedict's qualitative test, were used for the study. No adverse effect was observed at the tested concentration throughout the study.

**Experimental design**

Five groups of 6 rats each were used in this experiment. Group 1, normal control (the animals were given normal saline only). Group 2, diabetic group induced by streptozotocin (60 mg/kg bw). Group 3, treatment group diabetic animals treated with *P. boergesenii* aqueous extract at 400 mg/kg bw (effective dose of the extract). Group 4, Positive control (the diabetic ratstreated with glibenclamide at 2 mg/kg bw). Group 5, control (animals were treated with *P. boergesenii* at 400 mg/kg bw.[13] The animals were weighed and dose was given through oral intragastric tube every day. The test sample and reference standard drugs were given orally and the experiment was terminated in overnight fasted rats at the end of 30 days. After the experimental regimen, the animals were sacrificed by cervical dislocation after giving mild anesthesia using chloroform. Blood was collected using EDTA as the anticoagulant and serum was separated bycentrifugation at 2500 rpm. Liver and kidneys were immediatelydissected out, washed and stored in 0.9 % ice cold saline and weight was recorded. A 10 % homogenate of the liver and kidney tissue were prepared with 0.1 M Tris - HCL buffer, pH 7.4. The homogenates were used to analyze the enzyme activities and biochemical parameters.

**Analytical procedure**

The protein, urea, uric acid and creatinine were assayed according to the methods of Lowry et al., 1951,[14] Natelson et al., 1951,[15]Caraway *et al.*, 1963[16] and Brod *et al.*, 1964[17] respectively. Estimation of hemoglobin andglycosylated hemoglobin were estimated according to the standard methods (Saibene et al., 1979 and Drabkin et al., 1932).[18,19] The lipid profile oftotal cholesterol, free cholesterol, phospholipids, free fatty acids and triglycerides were calculated by the standard methods of Parekh and Jung, 1970,[20]Rouser *et al., 1970*,[21]Horn and Mehanan, 1981[22]and Rice, 1970[23] respectively.

**Histopathological analysis**

All the group ofanimals were sacrificed at the close of the experiment and pancreases, live and kidney tissue of rats was exposed to histological studies. The study achieved by cutting 5µm sections of the tissues using a microtome and fixing in 10% formalin and staining with haemotoxylene and eosin.[24]

**Statistical analysis**

The results obtained were expressed as mean ± SD. The statistical comparison among the groups were performed with one-way ANOVA and DMRT using statistical package (SPSS version 10.0) at $p<0.05$.

**RESULTS**

The present study exhibited a sharp decline in total proteins in uncontrolled diabetic rats. In *P. boergesenii* aqueous extract and glibenclamide treated rats, there was an improvement in protein profile. Treatment with aqueous extract *P. boergesenii* showed significant increase.

**Table 1: Changes in the levels of protein, hemoglobin and glycosylated hemoglobin in STZ induced diabetic rats.**

| Groups | Protein* (g/100 ml) | Hemoglobin* (g/100 ml) | Glycosylated hemoglobin# (mg fructose/ hemoglobin) |
|---|---|---|---|
| Group I | 6.22 ± 0.07 [c] | 12.54 ±0.14 [c] | 0.15 ± 0.01 [a] |
| Group II | 4.90 ± 0.07 [a] | 9.10 ± 0.39 [a] | 0.26 ± 0.01 [c] |
| Group III | 6.22 ± 0.38 [c] | 12.46 ± 0.28 [c] | 0.15 ± 0.01 [a] |
| Group IV | 5.76 ± 0.24 [b] | 11.93 ± 0.37 [b] | 0.18 ± 0.01 [b] |
| Group V | 5.74 ± 0.20 [b] | 11.93 ± 0.58 [b] | 0.17 ± 0.01 [b] |

Values are expressed as mean ± SD (n=6); values not sharing a common letter; differ significantly at < 0.05 by DMRT. (* g/100 ml # mg fructose/ hemoglobin).

**Table 2: Changes in the levels of serum urea, uric acid and creatinine in STZ induced diabetic rats.**

| Groups | Urea* (mg /100 ml) | Uric acid* (mg /100 ml) | Creatinine* (mg /100 ml) |
|---|---|---|---|
| Group I | 47.97 ± 2.70 [a b] | 1.37 ± 0.10 [a] | 0.75 ± 0.04 [a] |
| Group II | 61.90 ± 2.56 [d] | 2.03 ± 0.10 [c] | 1.79 ± 0.09 [d] |
| Group III | 47.94 ± 3.01 [a] | 1.37 ± 0.06 [a] | 0.70 ± 0.02 [a] |
| Group IV | 51.34 ± 2.57 [c] | 1.53 ± 0.08 [b] | 1.03 ± 0.04 [c] |
| Group V | 51.35 ± 1.56 [b] | 1.54 ± 0.10 [b] | 0.95 ± 0.04 [b] |

Values are expressed as mean ± SD (n = 6); values not sharing a common letter; differ significantly at < 0.05 by DMRT. (* mg/ 100 ml).

In the hemoglobin level in diabetic rats. Mean elevation of hemoglobin observed was 12.46 ± 0.28in treated group (Table 1). Serum contents of renal markers, like urea, uric acid, and creatinine were significantly increased in Group II diabetic rats as compared to Group I

control rats (Table 2). Diabetic rats treated with*P. boergesenii* aqueous extract showed markedly decreased renal markers, which is closer to normal levels. However, non-significant decreases were observed in *P. boergesenii* aqueous extract alone treated rats (P<0.05).

**Table 3. Changes in the serum lipid profile levels in control and experimental rats.**

| Groups | Total cholesterol * | Free cholesterol * | Phospholipids* | Free fatty acids* | Triglycerides * |
|---|---|---|---|---|---|
| Group I | 77.86 ± 2.98 [a] | 8.57 ± 0.25 [a] | 98.83 ± 1.43 [a] | 95.99 ± 1.95 [a] | 59.51 ± 1.39 [a] |
| Group II | 148.16 ± 15.3 [d] | 15.70 ±0.62 [d] | 140.71 ±2.11 [c] | 174.32 ± 10.9 [c] | 106.65 ± 4.01 [c] |
| Group III | 76.26 ± 2.18 [a] | 8.42 ± 0.58 [a] | 97.42 ± 2.69 [a] | 96.98 ± 6.10 [a] | 60.23 ± 1.78 [a] |
| Group IV | 97.06 ± 5.10 [b] | 9.50 ± 0.54 [b] | 113.18 ±2.19 [b] | 118.35 ± 3.21 [b] | 71.74 ± 3.33 [b] |
| Group V | 99.44 ± 4.68 [c] | 10.12 ±0.43 [b] | 112.63 ± 2.1 [b] | 122.17 ± 6.90 [b] | 73.43 ± 2.16 [b] |

Values are mean ± SD (n=6), values not sharing a common letter differ significantly at <0.05 by DMRT. (* mg/100m).

The levels of serum total cholesterol, free cholesterol, ester cholesterol, free fatty acids, triglycerides and phospholipids in normal and experimental animals are summarized in (Table 3). A significant increase in the levels of serum cholesterol, free cholesterol, free fatty acids, triglycerides and phospholipids were observed in diabetic rats. Treatment with the *P. boergesenii* extract and glibenclamide significantly reduced the levels of lipids, when compared to the control rats (P <0.05).

**Table 4: Changes in the liver lipid profile levels in control and experimental rats**

**Values are mean ± SD (n=6), values not sharing a common letter differ significantly at <0.05 by DMRT. (* mg/100ml).**

| Groups | Total cholesterol * | Free cholesterol * | Phospholipids* | Free fatty acids * | Triglycerides* |
|---|---|---|---|---|---|
| Group I | 2.58 ± 0.12 [a] | 1.06 ± 0.01 [a] | 16.03 ± 0.21 [a] | 7.54 ± 0.31 [a] | 3.88 ± 0.07 [a] |
| Group II | 5.00 ± 0.29 [c] | 1.76 ± 0.03[d] | 18.98 ± 12.91 [c] | 12.91 ± 0.46 [c] | 5.49 ± 0.23 [c] |
| Group III | 2.63 ± 0.14 [a] | 1.06 ± 0.05 [a] | 16.02 ± 0.16 [a] | 7.59 ± 0.49 [a] | 3.82 ± 0.12 [a] |
| Group IV | 3.27 ± 0.176 [b] | 1.35 ± 0.92 [b] | 17.03 ± 0.31 [b] | 8.03 ± 0.46 [b] | 4.35 ± 0.07 [b] |
| Group V | 3.54 ± 0.14 [c] | 1.43 ± 0.07 [c] | 17.03 ± 0.11 [b] | 8.13 ± 0.59 [b] | 4.39 ± 0.12 [b] |

**Table 5: Changes in the kidney lipid profile levels in control and experimental rats.**

| Groups | Total cholesterol * | Free cholesterol * | Phospholipids* | Free fatty acids* | Triglycerides* |
|---|---|---|---|---|---|
| Group I | 3.37 ± 0.11 [a] | 0.96 ± 0.03 [a] | 15.40 ± 0.21 [a] | 6.54 ± 0.2 [a] | 3.69 ± 0.09 [a] |
| Group II | 5.95 ± 0.18 [c] | 1.70 ± 0.02 [d] | 17.30 ± 0.69 [c] | 13.05 ± 0.53 [c] | 5.27 ± 0.12 [c] |
| Group III | 3.36 ± 0.17 [a] | 0.96 ± 0.05 [a] | 15.38 ± 0.38 [a] | 6.62 ± 0.30 [a] | 3.66 ± 0.10 [a] |
| Group IV | 3.84 ± 0.13 [b] | 1.16 ± 0.68 [b] | 16.14 ± 0.40 [b] | 7.26 ± 0.43 [b] | 4.15 ± 0.09 [b] |
| Group V | 3.72 ± 0.40 [b] | 1.23 ± 0.06 [c] | 16.09 ± 0.31 [b] | 7.36 ± 0.37 [b] | 4.26 ± 0.08 [b] |

Values are expressed ± SD (n=6), values not sharing a common letter differ significantly at < 0.05 by DMRT. (* mg/tissue).

(Table 4 and 5) represents the levels of total cholesterol, free cholesterol, free fatty acids, triglycerides and phospholipids in liver and kidney of normal and experimental rats. Oral administration of *P. boergesenii* extract significantly lowered the levels of total cholesterol, free cholesterol, ester cholesterol, free fatty acids, triglycerides and phospholipids as compared to Group II animals (P <0.05). Treatment of diabetic rats with Glibenclamide also lowered the tissue level of total cholesterol, free cholesterol, ester cholesterol, free fatty acids, triglycerides and phospholipids.

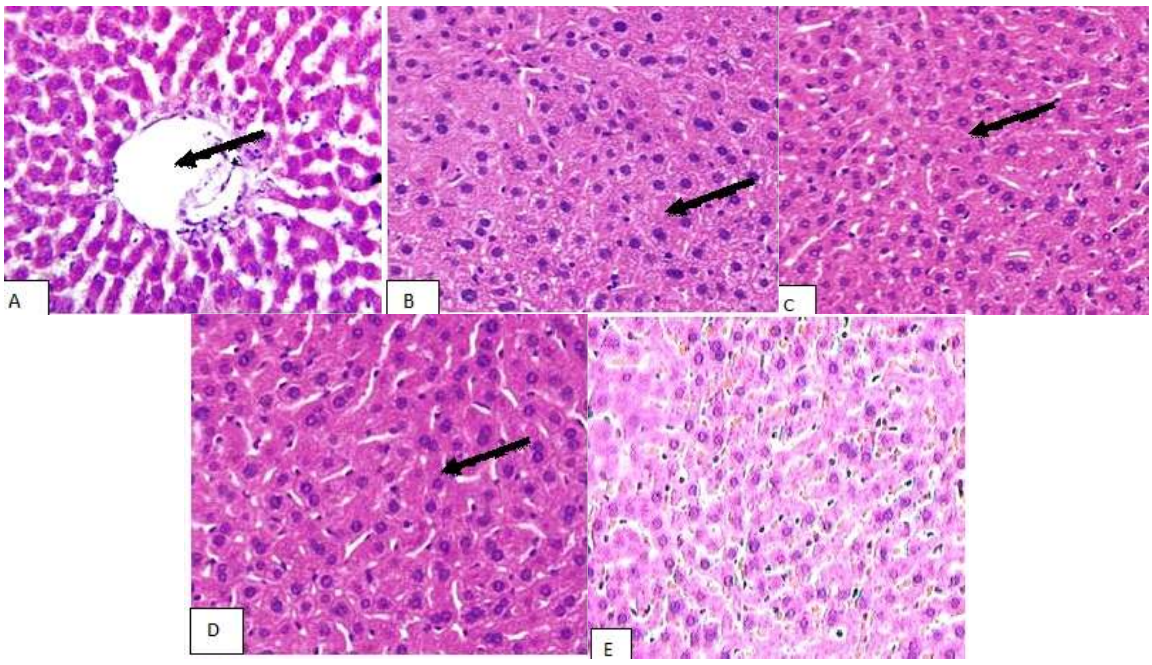


**Fig. 1: Liver histology in experimental rats.**

(A) Normal liver showing the central vein (CV),with radiating cords of hepatocytes; (B) Diabetic liver shows Macro vesicular steatiosis (MVS); (C) Conjugated and edementous Poratal vein (PV); (D) Poratal tract showing normal features with mild hemorrage ; (E) Group V. showing normal portal tract (PT)

The histopathological examination of liver in normal portal tracts of all three zones. The hepatic sinusoids and kuppfer cells showed preserved cytoplasm, nucleus and central veins whereas the streptozotocin induced rat liver tissue section shows distortion in the arrangement of cells around the central vein-periportal fatty infiltration with focal necrosis of hepatocytes (Fig. 1A and 1B). The *P. boergesenii* extract and glibenclamide treatment brought back the cellular arrangement around the central vein and reduced necrosis. It also helped to bring the blood vessels to normal condition (Fig. 1C and 1D). The Group V did not show any significant change of liver, when compared with Group I (Fig. 1E).

Histopathology of pancreas in normal tissues section shows lobules of exocrine acini, interlobular ducts and occasional islets of langerhan which is not observed in STZ induced diabetic pancreas (Fig. 2A and 2B). In *P. boergesenii* extract treated pancreas, the cells seem to have gathered together and small preserved islets similar to the normal (Fig. 2C and 2D). The Group V did not show any significant change of pancreas, when compared with normal pancreas (Fig. 2E).

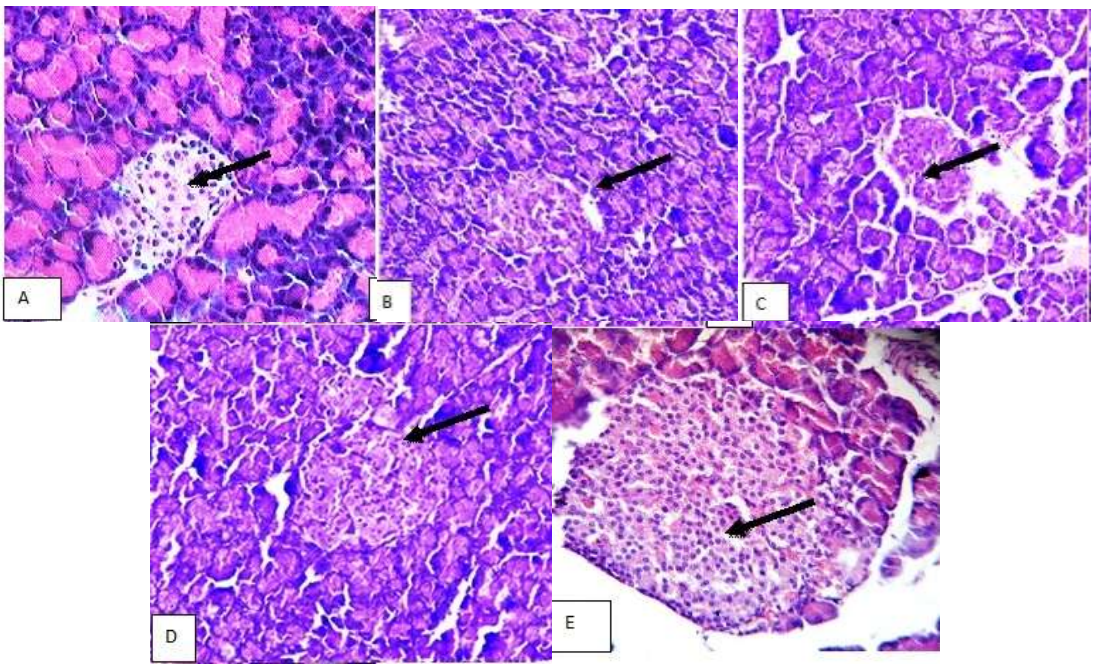


**Fig. 2: Pancreatic histology in experimental rats.**

(A) Pancreas shows exocrine acini and endocrineIslets (IL); (B) Shows depleted isletes (DIL); (C) Shows exocrine acini and small preserved islets; (D) Shows exocrine acini; (E) pancreas shows acini scatted islet cells.

Histological examination of renal section of the control rats showed (Fig. 3) the glomeruli, tubules, interstitium and blood vessels appear normal. Kidney sections of rats treated with streptozotocin shows tubular damage proteinurea and haemorrhage. In the case of *P. boergesenii*extract treated diabetic rats and diabetic rats treated with glibenclamide

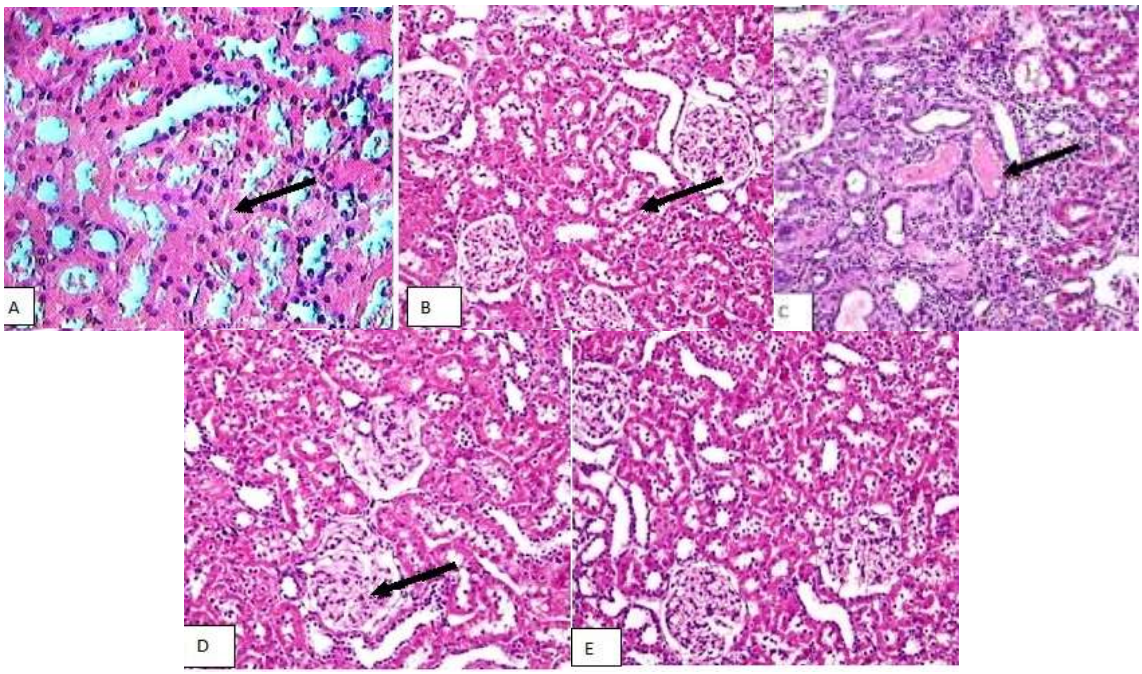


**Fig. 3: Kidney histology in experimental rats.**

(A) Normal kidney shows glomorulin (GM) andProximal convoluted tubules;

(B) Shows tubular damage proteinurea and homorrage;

(C) Shows glomoruli, tubules interstitium and blood vessels appear normal;

(D) Shows glomoruli, tubules without proteiurea and homorrage;

(E) Shows normal structure, shows the glomeruli, tubules, interstitium and blood vessels appear normal. The *P. boergesenii* extracts alone treated group showed normal structure comparable to the control group.

## DISCUSSIONS

In *P. boergesenii* extract and Glibenclamide treated rats, there was an improvement in protein profile which may be due to marked change in circulating amino acid level, hepatic amino acid uptake and muscle output of amino acid concentrations.[25]This may be due to decline in either albumin or globulin or both, hypoalbuminemia is a common problem in diabetic animals and it's generally attributed to the presence of nephropathy.[26] Hemoglobin leads to formation of glycohemoglobin throughout the circulatory life of RBC by addition of glucose

to N-terminal of hemoglobin beta chain. This process is non-enzymatic and reflects the average exposure of hemoglobin to glucose over an extended period.[27]

Treatment with *P. boergesenii* extract showed significant increase in the hemoglobin level in diabetic rats. Mean elevation of hemoglobin observed was 12.46 ± 0.28 in *P. boergesenii* treated group. The hemoglobin level was decreased in diabetic rats that may increase the formation of glycosylated hemoglobin. Glycosylated hemoglobin was found to increase in diabetic mellitus and the amount of increase is directly proportional to that of fasting blood glucose level.[28]

In the present study, administration of *P. boergesenii* extracts to diabetic rats reduced the elevated levels of urea, uric acid and creatinine to normal; this shows the normalizing effect of the seaweed extract on urea and creatinine synthesis.The increase in serum creatinine and urea levels in Streptozotocin induced diabetic rats may be due to hyperglycemia that causes osmatic diuresis and depletion of extracellular fluid volume. Several studies have shown an increased correlation between serum creatinine and urea in diabetic patients.[29]

Insulin plays an important role in metabolism of lipids; insulin is potent inhibitor of lipolysis. It inhibits the activities of hormone sensitive lipases in adipose tissue and suppresses the release of free fatty acids.[30] The antihyperglycemic effect of *P. boergesenii* extract may be due to the down regulation of NADPH and NADH, a cofactor in the fat metabolism. Higher activity of Glucose-6-phosphatase provides H+ which binds with NADP+ in the synthesis of fats from carbohydrates. When glycolysis slows down because of cellular activity, the pentose phosphate pathway still remains active in live to breakdown glucose that continuously provides NADPH which converts acetyl radicals into long fatty acid chains. The *P. boergesenii* extract might be the capable of oxidizing NADPH. Abnormalities in lipid profile are one of the most common complications in diabetes mellitus and cardiomyopathy. Acute insulin deficiency initially causes an increase in free fatty acid mobilization from adipose tissue.[31] Excess of fatty acids in serum of the Streptozotocin induced diabetes promotes conversion of excess fatty acids into phospholipids and cholesterol in liver. These two substances along with excess triglycerides formed in liver may be discharged into blood in the form of lipoproteins.[32]

The therapeutic effect of *P. boergesenii* was confirmed by histopathological study of the liver, pancreases and kidney from rats showed significant changes in the tissue morphology.

The histopathological changes in the liver, pancreases and kidney in diabetic rats treated with aqueous extract of *P. boergesenii* restore the normal structure. Consequently, seaweed *P. boergesenii* accomplished of reduction oxidative stress and restore tissue damage and increase activities of endogenous antioxidant enzymes in diabetic animals. Therefore, *P. boergesenii* may have therapeutic benefits effect. The outcome of the histopathological study was agreement with Balasee et al., 1972[33], reported that *P. boergesenii* have protective effect with reduced histopathological changes.

## CONCLUSION

In conclusion, the results of the present study show that *P. boergesenii*extract showed potent antidiabetic activity in STZ induced diabetic rats. The effective dose of *P. boergesenii*extract was found to be 400 mg/kg body weight. The action of *P. boergesenii* was comparable with antidiabetic drug glibenclamide. Results of this experimental study indicated that *P. boergesenii* has potent antidiabetic activity in STZ-induced experimental diabetes in rats. *P. boergesenii* appears to have a favorable significance for the increase of a potent phytomedicine from marine flora for diabetes, however more inclusive pharmacological studies are required to elucidate the exact mechanism of actionof the *P. boergesenii*extract.

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