

Antidiabetic Effect of *Hellenia speciosa* (J. Koenig) S. R. Dutta in Alloxan Induced Diabetic Rats

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ABSTRACT

Hellenia speciosa is a member of costaceae family and is used for the treatment of diabetes in Southern Indian. The present study was carried out to evaluate the antidiabetic effect of *Hellenia speciosa* leaves in normal and alloxan induced diabetic rats. The oral administration of crude leaf extract in diabetic rats for 28 days at a dosage of 300mg/kg body weight exhibited a significant reduction ($P < 0.05$) in fasting blood glucose level and a remarkable increase in serum insulin level. There was a significant reduction ($P < 0.05$) in total cholesterol, triglyceride, urea, aspartate transaminase, alanine transaminase, alkaline phosphatase and gamma glutamyl transferase in diabetic rats treated with *Hellenia speciosa* leaf extract. No significant change in serum sodium level, potassium level, chloride level and calcium level in diabetic rats when compared with control and experimental groups of rats. This shows that leaf is nontoxic and regenerates the toxic effect induced by alloxan. Based on the above results, it is evident that the leaves of *Hellenia speciosa* have antidiabetic effect and can be considered as an effective formulation for future studies. Histopathological studies reinforce the healing power of *Hellenia speciosa* in the liver and kidney tissues, as a possible mechanism of their antidiabetic activity.

Key Words: *Hellenia speciosa*, alloxan, antidiabetic activity, costaceae.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by multiple defect in pathophysiology and abnormalities in carbohydrate, protein and lipid metabolism. [1] Diabetes is caused by inherited or acquired deficiency of insulin produced or inefficiency of the insulin. [2] It is evident that disease leads to many complications such as hyperlipidemia, hypertension, atherosclerosis, retinopathy, neuropathy and nephropathy. [3,4] The modern system of medicine fails in providing a suitable medicament for diabetes mellitus, in spite of tremendous

advances made in discovery of new compounds. In diabetic patients about 70-80% of deaths are due to vascular disease. An ideal treatment for diabetes would be a drug that not only controls the glycemic level but also prevents the development of arteriosclerosis and other complications of diabetes. [5] Many herbs and plant products have been shown to have antihyperglycemic and antihyperlipidemic action. [6-8]

Medicinal plants establish a good relationship with human with its pharmacological action. In India the clinical use of plants for curing various diseases was practiced since during the vedic period of

India. The use of medicinal plants for curing many diseases gained importance because of its properties such as the effectiveness, low cost and less side effects. [9] The demands for medicinal plants are increasing and plays an important role in health care management. [10,11] More than 7500 plants are used as herbal medicine in India to cure ailments. [12] The presence of free radical scavenging property of the medicinal plants reduces the risk of various complications associated with diabetes. [13]

The plant *Hellenia speciosa* is a member of the family Costaceae and is a newly introduced plant in India. [14] It is an ornamental, perennial, succulent rhizomatous herb grown up to 2.7 meters in a moist, clayey soil under moderate shade. [15] The plant reproduces vegetative by stem cutting, rhizomes or division of clumps. The leaves of the plant are oblong, thick, spirally arranged, flowers large white cone like terminal spikes with bright red bracts. [16] Several studies were carried out on rhizome of *Hellenia speciosa* for its antimicrobial, anti-inflammatory, antidiabetic activities; but the studies on the medicinal properties of the leaf is lacking. The present study was conducted to investigate the antidiabetic activity of *Hellenia speciosa* leaf extract in alloxan induced diabetic rats.

MATERIALS AND METHODS

Plant material: *Hellenia speciosa* was collected from Thrissur district of Kerala and identified and confirmed by the botanist Dr. S. Ravikumar, PG and Research department of Plant Biology and Biotechnology, Presidency College, Chennai.

Preparation of plant extract: Preparation of extracts was done according to the combination of the methods used by Pizzale et al [17] and Lu and Foo. [18] About 1g of fleshy dried powder of *Hellenia speciosa* and plant materials were extracted with 20 ml ethanol 75%, acetone, chloroform, aqueous and petroleum ether (Merck, extra pure) for 1 min using an Ultra Turax mixer (13,000 rpm) and soaked overnight at room

temperature. The sample was then filtered through Whatman No. 1 paper in a Buchner funnel. The filtered solution was evaporated under vacuum in a rota-evaporator at 40 °C to a constant weight and then dissolved in respective solvents. The dissolving rate of the crude extracts was approximately 100 %. The solution was stored at 18 °C until use.

Animals: Adult Sprague dawley rats (100-140g) were purchased from Biogen, Bangalore, India were used for the study. All animals were housed 6/cage and kept in the animal house for one week for proper acclimatization under controlled condition of illumination (12 hours light / 12 hours darkness) and temperature ranging 20- 25 C and fed on standard pellet diet and water/ filtered water ad libitum. Ethical clearance for handling of experimental animals was obtained from Institutional Animal Ethics Committee (IAEC) constituted for the purpose and care of laboratory animals and taken as per guidance of the Committee for Purpose of Control and Supervision on Experiments on Animals (CPCSEA No. : 971/bc/06/CPCSEA)

Alloxan induced diabetic study was carried out by the method described by Nandhakumar et al [19]

Chemicals Required: The chemical and drugs used in the study were plant extract, alloxan, glucose, carboxymethyl cellulose (CMC), metformin, isoflurane (anaesthetic agent) was purchased from Sigma–Aldrich, St. Louis, MO, USA. Animal restrainer (e.g., Broom restraint, Plas Labs), Micrometer, glucometer (Accu-Check, Roche, Germany)

Induction of Diabetes Mellitus

After one week of the acclimatization, rats were injected once with low-dose of alloxan (80mg/kg) to induce partial insulin deficiency. The glucose value was noted using glucometer before alloxan injection. This is called as Basal value. After 48-96 hours of alloxan injection, the rat's fasting blood glucose values

(glucometer) were noted using tail flick method. The animals would display hyperglycemia and glucose intolerance. Animals with similar degrees of hyperglycemia (mostly above 95mg/dl) were considered.

Experimental design

According to their glucose value, animals were randomized and divided to groups as follows

- Group 1 – Normal Group
- Group 2 - Vehicle control (Untreated)
- Group 3 - Diabetic control (Untreated)
- Group 4 - Diabetic group + Metformin (350 mg/kg, p.o),
- Group 5 - Diabetic group + *Hellenia speciosa* (300mg/kg)

Animal blood collection

Animals were kept fasting for 12 hours on the day before glucose estimation. Then the animals tail were flicked, fasting blood parameters were noted on the Day 0 and every week (week 1, 2, 3 and 4) of the entire observation period.

Biochemical Analysis

The metabolic markers associated mainly with diabetes Plasma glucose, Insulin, Total cholesterol, Triglycerides, Total protein, Albumin, Globulin, Urea, Creatinine, Gamma glutamyl transpeptidase (GGT), Alanine Transaminase (ALT), Aspartate transaminase (AST), Calcium (Ca), Sodium (Na), Potassium (K), chloride (Cl), were analyzed using automated analyzers (Dimension Xpand Plus, Siemens)

Histopathology of Liver and kidney

The isolated Liver and kidney tissues fixed in 10% neutral-buffered formalin, dehydrated by passing through a

graded series of alcohol, and embedded in paraffin blocks and 5µm sections were prepared using a semi-automated rotary microtome (model RM2245, Leica Microsystems, Wetzlar, Germany). The sections were stained in hematoxylin and eosin. The sections were mounted by Disterene Phthalate Xylene (D.P.X.)

Statistical Analysis

Statistical comparison was done using one-way ANOVA followed by Dunnett's post hoc comparison when more than two groups are involved. P value less than 0.05 was considered significant.

RESULTS

In the present study following the alloxan treatment the glucose level, insulin, total cholesterol, triglyceride, total protein, urea, creatinine, marker enzymes and electrolytes showed significant alterations in diabetic rats. Their alterations may be due to impaired insulin signaling in diabetes. Administration of alloxan has caused significant elevation in glucose level when compared to control rats. Alloxan destroys the beta cells of Islets of Langerhans and causes reduced insulin secretion indicating hyperglycemia. [20]

Glucose and Insulin Level.

The blood glucose level of diabetic group was significantly higher (P<0.05) than that of Normal. The results showed a significant (P<0.05) reduction in blood glucose in *Hellenia speciosa* (300 mg/kg) treated groups compared with diabetic untreated group. The blood glucose of *Hellenia speciosa* treated groups was comparable with that of Metformin group at the end of the experiment.

Table 1 Effect of crude leaf extract of *Hellenia speciosa* on Glucose level and Insulin level in control and experimental rats

Groups	Glucose level(mg/dl)	Insulin level(µU/l)
Normal control	81.17 ± 4.17	25.2 ±0.8
Diabetic control	158.83 ± 16.20*	13.2 ±0.9*
Diabetic Vehicle control	156.50± 12.0	13.8 ±0.6
Metformin (350mg/kg)	121.67 ± 10.35	24.0 ± 1.3
<i>Hellenia speciosa</i> (300mg/kg)	133.83 ± 8.86 [#]	21.1 ±0.7 [#]

Values are expressed as Mean (n=6) ± Standard deviation *P<0.05 as compared to normal control and [#]P<0.05 compared to diabetic control

Total cholesterol and triglyceride

Increase in total cholesterol and triglyceride is the most common abnormalities found in diabetes. A significant ($p < 0.05$) increase in serum levels of total cholesterol and triglyceride was observed in diabetic rats when compared with normal rats whereas metformin and *Hellenia speciosa* treated rats showed significant ($p < 0.05$) reduction in the levels of total cholesterol and triglyceride.

Table 2 Effect of crude leaf extract of *Hellenia speciosa* on total Cholesterol, triglyceride level in control and experimental rats levels

Groups	Total cholesterol (mg/dl)	Triglyceride (mg/dl)
Normal control	116.83 ± 13.8	110.50 ± 27.11
Diabetic control	130.50 ± 18.3*	144.00 ± 15.27*
Diabetic Vehicle control	129.67 ± 20.0	140.67 ± 13.79
Metformin (350mg/kg)	119.17 ± 9.2	112.83 ± 19.9
<i>Hellenia speciosa</i> (300mg/kg)	124.83 ± 11.6 [#]	124.83 ± 11.63 [#]

Values are expressed as Mean (n=6) ± Standard deviation * $P < 0.05$ as compared to normal control and [#] $P < 0.05$ compared to diabetic control

Total protein, albumin, globulin, urea and creatinine levels

In diabetes protein degradation occurs due to insulin deficiency. This is evident from the present study (Table 3). A significant decrease ($P < 0.05$) in protein level was observed in alloxan induced diabetic model rats compared with control rats The slight decrease in level of albumin and globulin were observed in diabetic and diabetic vehicle when compared to the normal group. A significant decrease ($P < 0.05$) was noted for albumin and globulin. The conditions were reversed in Metformin and *Hellenia speciosa* treated groups.

Table 3 Effect of crude leaf extract of *Hellenia speciosa* on total protein, albumin and globulin levels in control and experimental rats

Groups	Total Protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	Urea (mg/dl)	Creatinine (mg/dl)
Normal control	6.6 ± 0.4	4.2 ± 0.2	5.4 ± 0.5	24±1.67	0.7±0.1
Diabetic control	3.1 ± 0.5*	1.8 ± 0.3*	4.5 ± 0.5*	44.33±2.78*	0.9±0.1
Diabetic Vehicle control	3.2 ± 0.4	1.7 ± 0.3	4.5± 0.5	44.33±2.58	0.9±0.1
Metformin (350mg/kg)	6.6 ± 0.2	4.0 ± 0.2	5.0 ± 0.5	28.67±1.51	0.8±0.1
<i>Hellenia speciosa</i> (300mg/kg)	6.8 ± 0.2 [#]	4.4± 0.3 [#]	5.4 ± 0.5 [#]	24.33±1.37 [#]	0.8±0.1

Values are expressed as Mean (n=6) ± Standard deviation * $P < 0.05$ as compared to normal control and [#] $P < 0.05$ compared to diabetic control

Marker enzymes

Table 4 Effect of crude leaf extract of *Hellenia speciosa* on marker enzymes in control and experimental rats

Groups	ALP (IU/I)	ALT (IU/I)	AST (IU/I)	GGT (IU/I)
Normal control	132.2 ± 22.8	46.0 ± 4.8	56.0 ± 2.2	8.30 ± 0.81
Diabetic control	192.0 ± 32.6	54.2 ± 5.9	72.0 ± 4.2	12.20 ± 0.90
Diabetic Vehicle control	193.0 ± 18.1	54.0 ± 2.6	72.3 ± 16.6	12.96 ± 1.50
Metformin 350mg/kg	142.5 ± 8.7	50.2 ± 5.2	60.0 ± 5.8	10.48 ± 0.52
<i>Hellenia speciosa</i> (300 mg/kg)	162.5 ± 16.5	45.2 ± 6.6	58.0 ± 13.0	9.00 ± 0.81

Values are expressed as Mean (n=6) ± Standard deviation * $P < 0.05$ as compared to normal control and [#] $P < 0.05$ compared to diabetic control

The results of fluctuations in marker enzymes are tabulated in the Table 4. Marker enzymes such as ALP, ALT, AST and GGT were found to be significantly ($P < 0.05$) elevated in the serum of alloxan induced diabetic rats when compared to normal control. Administration of *Hellenia speciosa* exhibited a significant ($P < 0.05$)

decrease in the levels of these marker enzymes (ALP, ALT, AST and GGT) when compared with diabetic control group. Metformin treated rats also showed significant reduction in the levels of marker enzymes.

Electrolytes

Table 5 shows the levels of electrolytes in control and experimental animals. The results obtained in the present study do not show any significant variations

in the diabetic rat when compared with normal control. Treatment with *Hellenia speciosa* and metformin also does not elicit significant change.

Table 5 Effect of crude leaf extract of *Hellenia speciosa* on electrolytes level in control and experimental rats

Groups	Sodium (mEq/l)	Potassium (mEq/l)	Chloride (mEq/l)	Calcium (mEq/l)
Normal control	135.20 ± 0.7	2.80 ± 0.2	102.7 ± 2.0	9.9 ± 4.8
Diabetic control	135.9 ± 1.0 ^{NS}	2.80 ± 0.3 ^{NS}	102.9 ± 2.2 ^{NS}	8.9 ± 3.8 ^{NS}
Diabetic Vehicle control	135.3 ± 1.1	2.87 ± 0.2	102.8 ± 2.1	8.5 ± 0.5
Metformin 350mg/kg	135.8 ± 3.2	2.80 ± 0.3	102.6 ± 2.0	8.8 ± 0.7
<i>Hellenia speciosa</i> (300 mg/kg)	135.0 ± 2.7 ^{NS}	2.8 ± 0.03 ^{NS}	102.2 ± 1.4 ^{NS}	8.5 ± 0.7 ^{NS}

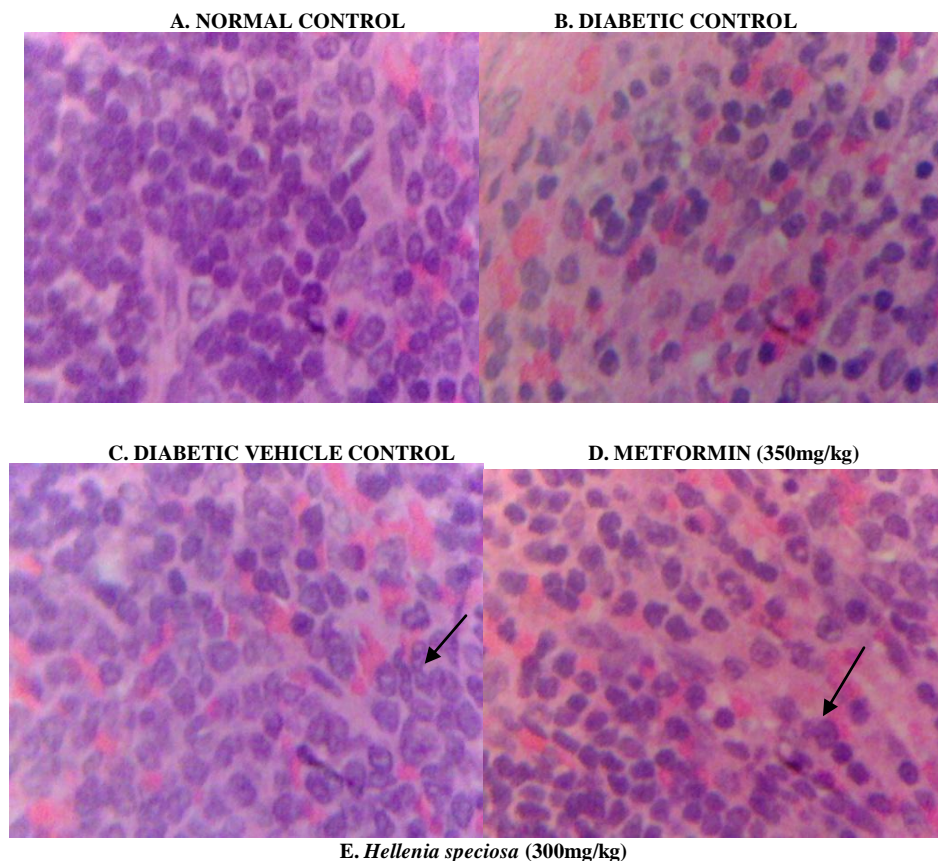
Values are expressed as Mean (n=6) ± Standard deviation *P<0.05 as compared to normal control and #P<0.05 compared to diabetic control, NS- No significance.

Kidney morphology

Histopathological examination of the kidney of the control rats showed normal histology with numerous glomeruli, renal tubules and blood vessels. Alloxan induced diabetic rats disclosed damaged blood vessels with interstitial large space when comparison with normal control. Administration of *Hellenia speciosa* extract reversed the structural changes to near normal architecture (Plate 1 Figure A-E).

Liver morphology

Photomicrograph sections of liver tissues of diabetic rats showed distortion of normal architecture with congestion of blood vessels, dilation of blood sinusoids and vacuolar degeneration. Whereas treatment with *Hellenia speciosa* extract for 28 days retrieved the normal morphology by reducing the vacuolar damage (Plate 2 Figure A-E)



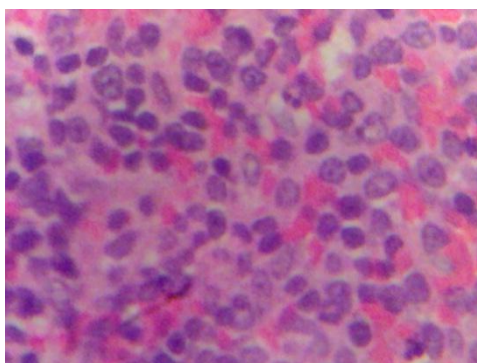
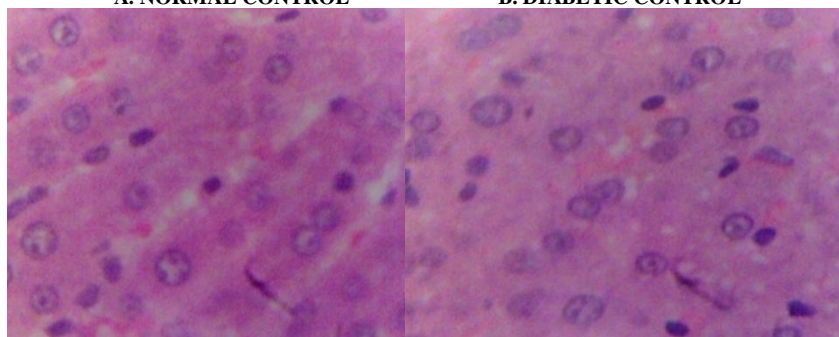


Plate1 Histopathology of kidney

- A. Kidney tissue of normal rats
- B. Kidney tissue of diabetic rats showing damaged cells and vacuoles
- C. Kidney tissue of diabetic vehicle control rat showing damaged cells and vacuoles
- D. Kidney tissue of metformin treated rats showing mild damage with less vacuoles
- E. Kidney tissue of rats treated with *Hellenia speciosa* showing near normal architecture

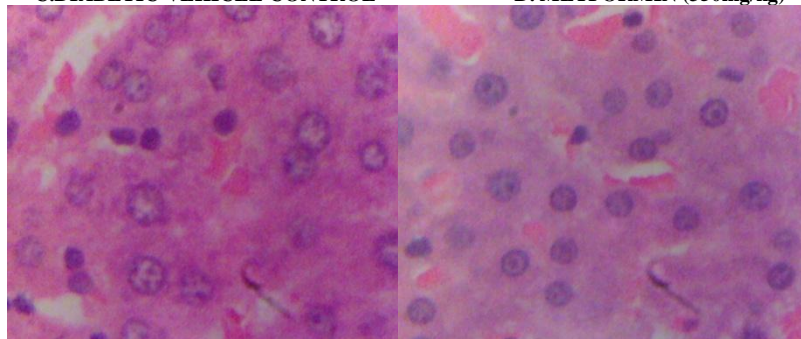
A. NORMAL CONTROL

B. DIABETIC CONTROL



C. DIABETIC VEHICLE CONTROL

D. METFORMIN (350mg/kg)



E. *Hellenia speciosa* (300mg/kg)

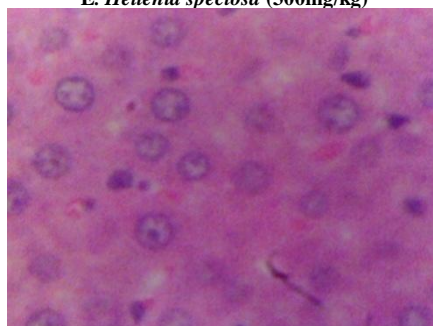


Plate 2 Histopathology of liver

- A. Hepatic tissue of normal control rats
- B. Hepatic tissue of diabetic rats showing destruction of hepatocytes and vacuolation
- C. Hepatic tissue of diabetic vehicle control rat showing destruction of hepatocytes and vacuolation
- D. Hepatic tissue of rats treated with metformin showing fatty changes, necrosis and congestion
- E. Hepatic tissue of rats treated with *Hellenia speciosa* showing mild fatty changes and congestion.

DISCUSSION

Effect of crude extract of *Hellenia speciosa* on Glucose and Insulin Level.

The blood glucose level of diabetic group was significantly higher ($P < 0.05$) than that of Normal. The results showed a significant ($P < 0.05$) reduction in blood glucose in *Hellenia speciosa* (300 mg/kg) treated groups compared with diabetic untreated group. The results from this study indicated that the plasma insulin level of diabetic group was significantly ($P < 0.05$) reduced when compared with Normal group. The results show an increase in plasma insulin levels of diabetic rats treated with *Hellenia speciosa*. (300 mg/kg). *Hellenia speciosa* significantly ($P < 0.05$) attenuated alloxan-induced hypoinsulinaemia. The hypoglycemic effect of *Hellenia speciosa* may be due to its insulin secretory effect on the beta cells of Islets of Langerhans of pancreas. Metformin treated rats also showed significant glucose lowering effect. The results obtained in the present study are in correlation with Eliza et al [21] (Table 1)

Effect of crude extract of *Hellenia speciosa* on total cholesterol and triglyceride levels

Increase in total cholesterol and triglyceride is the most common abnormalities found in diabetes. A significant ($p < 0.05$) increase in serum levels of total cholesterol and triglyceride was observed in diabetic rats when compared with normal rats whereas metformin and *Hellenia speciosa* treated rats showed significant ($p < 0.05$) reduction in the levels of total cholesterol and triglyceride. Table 2 represents the levels of total cholesterol and triglycerides in control and experimental animals. The high levels of serum lipids in diabetic subjects are mainly due to increase mobilization of free fatty acids from peripheral fat depots. Acute insulin deficiency causes an increase in free fatty acid mobilization from the adipose tissues. This results in increased levels of lipids in serum. [22] Insulin deficiency also inactivates the enzymes lipoprotein lipase which in turn

promotes the conversion of free fatty acid to cholesterol and triglycerides which elevates in the serum. [23,24]

Effect of crude extract of *Hellenia speciosa* on total protein, albumin, globulin, urea and creatinine levels

In diabetes protein degradation occurs due to insulin deficiency. This is evident from the present study (Table 3). A significant decrease ($P < 0.05$) in protein level was observed in alloxan induced diabetic model rats compared with control rats. A significant decrease ($P < 0.05$) was noted for albumin and globulin in diabetic and diabetic vehicle when compared to the normal group. The conditions were reversed in Metformin and *Hellenia speciosa* treated groups. Decreased level of protein in diabetes is due to insulin deficiency which in turn causes excessive catabolism of protein and the amino acids released are used for gluconeogenesis. [25,26] Due to increase in protein degradation in diabetic group the blood urea was found to significant increase ($P < 0.05$) when compared to normal control.

However upon treatment with *Hellenia speciosa* the levels were found to decrease significantly ($P < 0.05$) when compared to diabetic control and almost reverted back to normal. No significant change in the levels of creatinine was observed among the experimental groups where as a mild fluctuations in the values are recorded in diabetic control and diabetic vehicle control.

Effect of crude extract of *Hellenia speciosa* on marker enzymes

The results of fluctuations in marker enzymes are tabulated in the Table 4. Marker enzymes such as ALP, ALT, AST and GGT were found to be significantly ($P < 0.05$) elevated in the serum of alloxan induced diabetic rats when compared to normal control. The increase in the level of these enzymes may be due to leakage of the enzyme from the cytosol into the blood stream. [27][28] The hepatocyte injury may be

attributed to the insulin resistance which induces excess free fatty acid synthesis. [29] Elevated transaminase activity in diabetic rats due to increased gluconeogenesis and ketogenesis. [30] Administration of *Hellenia speciosa* exhibited a significant ($P < 0.05$) decrease in the levels of these marker enzymes (ALP, ALT, AST and GGT) when compared with diabetic control group. Metformin treated rats also showed significant reduction in the levels of marker enzymes.

Effect of crude extract of *Hellenia speciosa* on Electrolytes

Electrolytes play an important role in body mechanism such as acid base balance, nerve conduction, blood clotting, malabsorption syndrome, muscle contraction and multidrug regimens. [31] Electrolyte imbalance is frequently observed in diabetes. Insulin deficiency, hyperglycemia and dehydration were the main causes for electrolyte disturbances. In diabetes electrolyte imbalance results from kidney failure and dehydration. [32] The study is focused on sodium, potassium, chloride and calcium which are considered as major electrolytes. In our study we observed mild fluctuation but no significant change in serum sodium level, potassium level, chloride level and calcium level in diabetic rats when compared with control and experimental groups of rats (Table 5) The results of the present study were in agreement with Stephen et al [33] Therefore, the present study does not show any significant alterations in electrolyte levels.

Histopathological studies

The histopathological examination revealed alterations in liver and kidney of alloxan induced diabetic rats. The liver of control rats shows normal architecture whereas the liver of diabetic rats shows fatty hepatocytes with inflammatory infiltrations. Histologically the liver section of alloxan induced diabetic rats showed marked structural alterations in the liver as a result of absence of insulin. The major alteration

was periportal fatty infiltration necrosis of hepatocytes. This damage is partially reversed by *Hellenia speciosa* leaf extract treatment and the results are similar to that observed by *Gymnema sylvestre* therapy in alloxan diabetic rabbits by Shanmugasundaram et al [34] and *Vinca rosea* extract in alloxan induced diabetic rats by Ghosh and Surawanshi [35] The liver of *Hellenia speciosa* treated rats showed normal architecture. Histopathology study of kidney of diabetic rats showed destruction of hepatocytes and vacuolation. The degenerative changes in the histology of liver and kidney induced by alloxan induced diabetes are similar to earlier reports. [36] [37] Another finding was that *Momordica charantia*, a diabetic plant administered for 10 days to diabetic rats improved the diabetes induced degenerative changes such as hypercellularity, inflammatory infiltrate and basement membrane thickening. The similar feature was observed in current study and treatment with *Hellenia speciosa* improved this condition. [38] This shows that the plant did not have any toxic effect.

The histopathological finding on kidney and liver tissues observed that even after 28 days of dosing restored the morphological changes indicating that medicinal plant *Hellenia speciosa* is renal protective and hepato protective.

CONCLUSION

The *Hellenia speciosa* leaf extract effectively reversed the alloxan induced changes in the blood sugar level and restored normal cell population in the liver. The results also suggest that the antidiabetic activity of *Hellenia speciosa* is comparable to the standard drug metformin. Thus the studies highlight the use of *Hellenia speciosa* as a potential herbal formulation in the treatment of diabetes.

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How to cite this article: Ramya R, Dhamotharan R. Antidiabetic effect of *Hellenia speciosa* (J. Koenig) S. R. Dutta in alloxan induced diabetic rats. Int J Health Sci Res. 2019; 9(8):19-28.
