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ANTI-DIABETIC PROPERTIES OF *LANNEA COROMANDELICA* L. BARK EXTRACT ON ALLOXAN INDUCED TYPE-2 DIABETIC RATS

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ABSTRACT

Background: Diabetes is a major public health concern. Despite of continuous new drug development, diabetes and its related complications remains to be a major clinical problem. Medicinal plants are efficient ameliorator of oxidative stress associated with diabetes mellitus and herbal remedies remain a potential adjunct therapy to maintain better glycemic control with a few side-effects. The aim of the present study was to investigate the antidiabetic activities of *Lannea coromandelica* L. bark (LC) in alloxan induced type-2 diabetic rats. **Methods:** Diabetes was induced by a single dose of intraperitoneal injection of alloxan (150mg/kg) in SD rats of either sex and was divided into 5 groups of 6 animals each. Ethanolic extract of barks from *Lannea coromandelica* (LC 250 and 500mg/kg) and glibenclamide (10mg/kg) were orally administered once daily for 21 days in the treatment and standard group respectively. Blood glucose levels were measured on 0, 7, 14 and 21 days of oral treatment. OGTT was performed on type-2 diabetic rats and at the end of the experiment, rats were sacrificed and blood samples were collected for the measurement of total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL) and high density lipoproteins (HDL), S. creatinine ALT and AST levels. **Results:** The results after 21 days of oral administration of LC at doses of 250 and 500mg/kg showed a significant attenuation in blood glucose level in both the acute ($p<0.001$) and chronic study ($p<0.001$), also significantly lowered TC ($p<0.001$), TG ($p<0.001$), LDL-C ($p<0.001$) levels and improved HDL-C insignificantly in diabetic rats. Oral ingestion of LC very highly significantly reduced the creatinine levels ($p<0.01$), ALT ($p<0.001$) and AST ($p<0.001$) when compared to vehicle treated diabetic control group. These results confirmed marked improvement of the destructive effect on pancreatic islet cells induced by alloxan. **Conclusion:** In conclusion, our findings illustrated that the ethanolic extract of LC barks possessed glucose and lipid lowering efficacy and it is due to the protective effect on pancreas, liver and kidney from oxidative damage in alloxan-induced diabetic rats. The study provides a scientific rationale for the use of *L. coromandelica* in the management of diabetes and its related complications. Further studies are recommended to evaluate the precise mechanisms of action and the potential of the plant.

KEYWORDS: Antidiabetic properties, *Lannea coromandelica*, antihyperlipidemic effect, alloxan induced diabetes, type-2 diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a metabolic disease with deficiency of secretion or action of endogenous insulin, features of hyperglycemia, and no definite cause (Paik SG, Blue ML, Fleischer N and Shin SI, 1982 and Kataoka S *et. al.*, 1983). Diabetes is a major risk factor for the development of cardiovascular disease. More than 70% of deaths in diabetic patients are due to vascular disease. One of the greatest factors in the development and progression of the complications of diabetes mellitus is hyperglycemia (Fiorentino TV, Prioletta A, Zuo P and Folli F, 2013). Hyperglycemia contributes to majority of diabetic complications by altering vascular Cellular metabolism, Vascular matrix molecules, and circulating lipoproteins (ADA, 2010). Treatment of diabetes involves use of drugs that reduce glucose levels, including insulin and oral antihyperglycemic drugs. Although there is treatment for diabetesmellitus, most drugs in current use are seriously constrained by both their side effects and cost of treatment. Due to these challenges, populations mainly in Sub-Saharan Africa have resorted to cheaper and readily available alternative sources of treatment, such as use of medicinal plants or traditional medicines (Modak M, Dixit P, Londhe J, Ghaskadbi S and Devasagayam TPA, 2007). The use of medicinal plants as food supplements and in the treatment of specific diseases dates back to antiquities. In actual facts, herbal preparations and their therapeutic

uses can be traced to the origin of man himself. Although several synthetic drugs are available, attention is currently being focused on the use of plants and plant products in prevention or correction of various metabolic disorders or in the treatment of specific diseases because of several side effects associated with the use of synthetic drugs (Oze G et. al., 2008 and Zhang J, Yulong H, Tiande H and Yunpu W, 2005). Several plants are now known to have medicinal effects across the different regions of the world. Some of these have been demonstrated to be of significant value in the treatment of diabetes and its complications (Saba AB, Oyagbemi AA and Azeez OI, 2010).

Lannea coromandelica Linn. Commonly known as 'Indian Ash tree' and also as 'Jiga' in Bengali is a medium size deciduous tree of anacardiaceae family and most widely distributed all over the Bangladesh, India and Africa. It is to 25 m high, bark surface grey to dark brown, rough, exfoliating in small irregular flakes, fibrous; blaze crimson red or deep pink; exudation gummy, red; young parts stellate-rusty tomentose (Jackson JK, 1994; The Plant List, 2010 and Jain SK, 1991). It contains flavonoids, alkaloids, glycosides, carbohydrate and phenolics (Jain SK, 1991). Many chemical constituents have been isolated from the plant. Major part of them is polyphenols including tannins like ellagic acid, gallic acid. and flavonoids like quercetin, kaempferol, isoquercetin. In addition, it also contains some sterols (Sankara Subramanian S and Nair AGR, 1971; Reddy AK, Joy JM and Kumar A, 2011). *L. coromandelica* has been reported to have anti-inflammatory (Saravanan S, Dhasarathan P, Indira V and Venkataraman R, 2010), anti-microbial, wound healing (Sathish R, Mohd HA, Natarajan K and Lalitha KG, 2010), hypotensive and aphrodisiac activities (Singh S and Singh GB , 1996), sore eyes, leprosy, sprains, bruises (Kirtikar KR and Basu BD, 2000), elephantiasis (Shah GL, Yadav SS, Badri N, 1983). It is also used in the treatment of coma caused by narcotics, general debility, and impotency (Jain SK, 1991).

The present study evaluated the antidiabetic properties of bark extract of *L. coromandelica* against alloxan induced type-2 diabetic rats.

MATERIAL AND METHODS

Plant collection and Extraction

The bark of *Lannea coromandelica* was collected, taxonomically identified and authenticated by the Bangladesh National Herbarium, Mirpur, Dhaka. The collected materials were shed dried at 35º – 40º C for a week and crushed into moderately coarse powder. This powder was extracted using ethanol, dried under reduced pressure and finally extract was obtained.

Experimental Animals

The study was conducted with adult Sprague Dawley (SD) rats (weighing 150-200g) of either sex. They were bred at the Jahangirnagar University animal house maintained at a constant room temperature of 22 ± 5^0C, 40-70% humidity conditions and the natural day-night cycle with an *ad libitum* access to food except the day of experimental procedure when animals were used after 12 hrs fasting. The rats had no access to food during the whole period of blood sampling. All protocols for animal experiment were approved by the institutional animal ethical committee.

Induction of Type 2 Diabetes

Rats were injected with a freshly prepared solution of alloxan monohydrate (i.p.) in saline (300 mM NaCl) at a dose of (150 mg/kg, b.w.). Alloxan injection can provoke fatal hypoglycemia as a result of reactive massive release of pancreatic insulin, so rats were also given orally 5–10 mL of a 20% glucose solution after 6 h. Rats were then kept for the next 24 h on a 5% glucose solution as beverage to prevent too severe hypoglycemia. After 1 week, rats displaying fasting glucose level 8-15 mmol/l were chosen for the experiments (Ben Abdallah KR, *et. al.*, 2015 and Leila Z *et. al.*, 2007).

Acute study

OGTT was conducted in control and treated groups of rats, 24 h before decapitation of rats. All groups were administrated glucose (3g/kg) by gastric gavages route. Blood glucose levels were determined at 0, 60 and 120 min subsequently to receive glucose and fasting glucose was measured (Jarald E, Joshi SB, and Jain DC, 2009).

Chronic study

Hyperglycaemic (Type-2) animals were then divided into five groups of six animals each. Group I and II were treated with saline and served as normal control and diabetic control. Group III was administered glibenclamide and served as standard. Group IV and V were administered ethanolic extract of *L. coromandelica* at 250mg/kg and 500mg/kg body weight by oral route. All doses were continued for 21 days in hyperglyceamic rats. Blood samples were collected from the cut tip of the tail at 0, 7, 14 and 21st day from the respective start of treatments and measured serum glucose. At the end of the experiment rats were sacrificed, blood was collected and serum lipid profile, creatinine, ALT and AST levels were estimated by enzymatic colorimetric method (Shah NA and Khan MR, 2014).

Biochemical analysis

Serum glucose was measured by glucose-oxidase-peroxidase method (GOD-POD) using a commercial kit (glucose kit, Randox™, UK). The total cholesterol, triglyceride (TG), HDL and LDL by enzymatic-colorimetric method (Ramadan BK, Schaalan MF and Tolba AM, 2017).

Statistical analysis

Graphs were prepared by using MS Excel 2007 and data analysis for animal studies were done by SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA) using the One way ANOVA followed by Bonferroni's post hoc

test. All the data were presented as Mean±SEM. *(P<0.05), **(p<0.01) and ***(p<0.001) were counted as significant, highly significant and very highly significant respectively as compared to the vehicle treated diabetic control group (Ramadan BK, Schaalan MF and Tolba AM, 2017).

RESULTS

Oral glucose tolerance test was carried out in glucose loaded diabetic animals. There was a marked change in glucose level in diabetic animals after administration of glucose. Glucose level continued to increase till 60 min after glucose administration in LC and diabetic control groups. At 120 min after glucose administration glucose level was observed to be reduced significantly by LC at 500mg/kg dose (*P*<0.001) showing antihyperglycemic effect (Table 1 and figure 1). Dose dependent effects were also observed for LC.

Treatment with *L. coromadelica* for 21 days improved the fasting glucose level. Treatment wih LC did not reduced FBG significantly till 7 days. At the day 14, LC 250mg/kg reduced FBG significantly (p<0.05) and LC 500mg/kg reduced highly significantly (p<0.01). At the day 21, the effect was observed highly significant at 250mg/kg (p<0.01) and very highly significant at 500mg/kg (p<0.001) respectively. Glibenclamide showed very highly significant effect (p<0.001) as compared to the vehicle treated diabetic control group (table 2 and figure 2).

Effect of administering LC to diabetic rats on serum lipids like TC, TG, LDL-C, and HDL-C were presented in tables 3 and figure 3. The rise in blood sugar is accompanied by the increase in TC, TG, LDL-C, and fall of HDL-C in diabetic rats. The levels of serum TC, TG and LDL-C were significantly (p<0.001) increased in diabetic rats when compared to those of normal control rats. The serum lipids like TC, TG and LDL-C were very highly significantly (p < 0.001) decreased by the treatment with LC 500mg/kg and HDL-C level was increased insignificantly as compared to the diabetic control group.

In this study, we observed an early attempt to rescue the renal damage of alloxan in diabetes by both the reference drug (glibenclamide) and LC extract (table 4 and figure 4). The serum creatinine level was decreased highly significantly (p<0.01) after 21 days treatment of LC at the dose of 500mg/kg.

The effects of *Lannea coromandelica* to diabetic rats on ALT and AST were presented in table 5 and figure 5. Alloxan administration increased liver function biomarkers such as ALT and AST in comparison with normal control rats. The enzymes levels were reduced by treating diabetic rats with LC for 21 days. At LC 250mg/kg, the reduction of ALT and AST were significant (P<0.05) and highly significant (p<0.01) respectively whereas at 500mg/kg, it was very highly significant (p<0.001) when compared to those of diabetic control rats. The standard drug glibenclamide at 10mg/kg dose reduced ALT and AST level very highly significantly (p<0.001).

Table 1: Effect of ethanolic extract of *L. coromandelica* (LC) on the glucose loaded type-2 diabetic rats (OGTT).

Group	Glucose level (mmol/l)		
	0 min	60 min	120 min
Normal Control	5.62±0.19	7.25±0.25	6.93±0.21
Diabetic Control	10.55±0.56†††	13.55±0.65†††	14.30±0.42†††
STD (Glibenclamide 10 mg/kg)	10.38±0.51	11.57±0.35	9.02±0.22***
LC 250mg/kg	10.47±0.69	12.85±0.65	11.20±0.41***
LC 500mg/kg	10.52±0.45	12.53±0.47	10.57±0.25***

N.B: Data were analyzed by one way ANOVA following Bonferroni post hoc test. Values are expressed as Mean±SEM, n=6. *(p< 0.05) = significant ** (p< 0.01) = highly significant, *** (p< 0.001) = very highly signifiLCnt compared to diabetic control. † (p<0.05), †† (p<0.01) and ††† (p<0.001) as compared to normal control group.

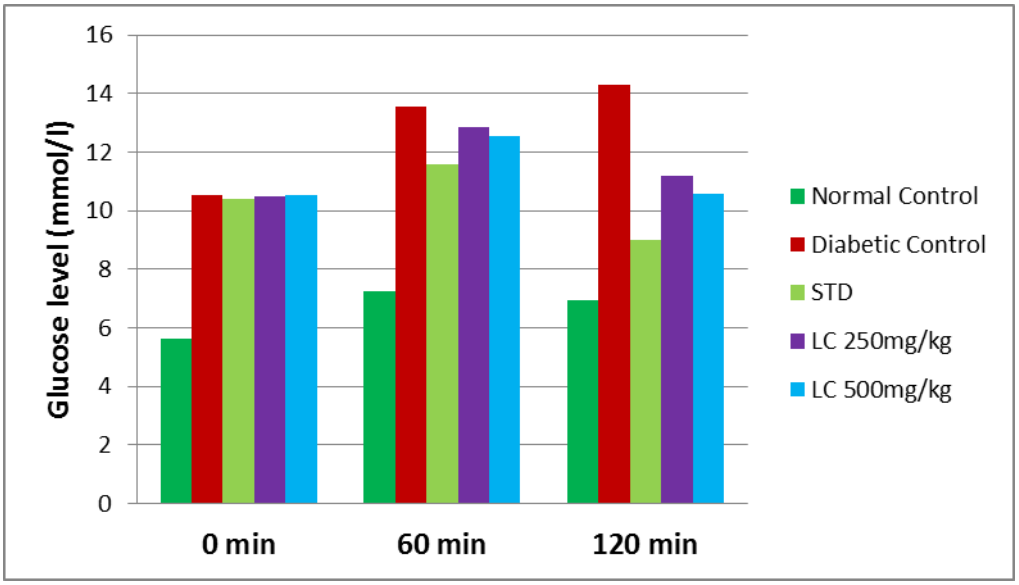

Figure 1: Effect of ethanolic extract of *L. coromandelica* (LC) on the glucose loaded type-2 diabetic rats (OGTT).

Table 2: Effect of ethanolic extract of *L. coromandelica* (LC) on the fasting blood glucose level after 21 days feeding in type-2 diabetic rats.

Group	Glucose level (mmol/l)			
	Day 0	Day 7	Day 14	Day 21
Normal Control	5.70±0.18	5.32±0.17	5.62±0.30	5.67±0.19
Diabetic Control	10.92±0.34†††	11.03±0.35†††	11.22±0.21†††	10.95±0.32†††
STD	10.75±0.52	9.73±0.55	8.78±0.40***	7.47±0.39***
LC 250mg/kg	10.83±0.26	10.33±0.30	9.92±0.31*	9.32±0.23**
LC 500mg/kg	10.78±0.34	10.42±0.38	9.40±0.20**	8.30±0.15***

N.B: Data were analyzed by one way ANOVA following Bonferroni post hoc test. Values are expressed as Mean±SEM, n=6. *(p< 0.05) = significant, ** (p< 0.01) = highly significant, *** (p< 0.001) = very highly signifiLCnt compared to diabetic control. † (p<0.05), †† (p<0.01) and ††† (p<0.001) as compared to normal control group.

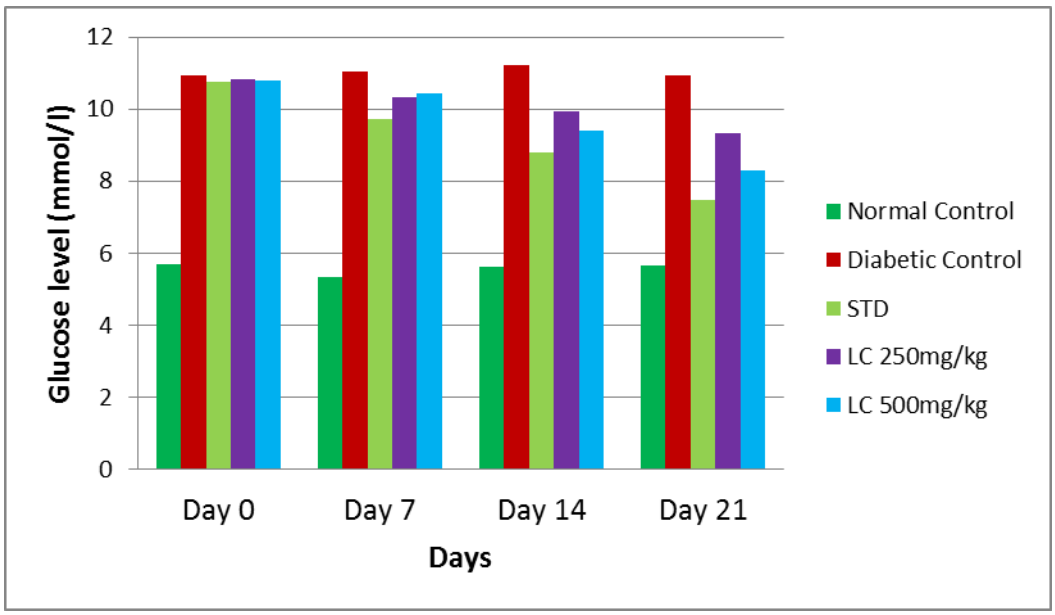

Figure 2: Effect of ethanolic extract of *L. coromandelica* (LC) on the fasting blood glucose level after 21 days feeding in type-2 diabetic rats.

Table 3: Effect of the ethanolic extract of *L. coromandelica* (LC) on total cholesterol (TC), triglycerides (TG), LDL-C and HDL-C level after 21 days feeding in type-2 diabetic rats.

Group	TC (mg/dl)	TG (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
Normal Control	137.83±4.29	126.67±5.25	109.17±4.05	40.00±2.97
Diabetic Control	208.83±5.26†††	188.50±4.08†††	256.33±5.77†††	25.17±1.89††
STD (Glibenclamide 10 mg/kg)	140.00±1.97***	139.67±3.95***	93.00±4.15***	44.67±2.26***
LC 250mg/kg	183.00±3.89**	171.83±4.77	192.67±3.60***	28.33±3.03
LC 500mg/kg	166.50±2.69***	150.83±3.10***	167.00±4.47***	33.33±1.38

N.B: Data were analyzed by one way ANOVA following Bonferroni post hoc test. Values are expressed as Mean±SEM, n=6. *(p< 0.05) = significant, ** (p< 0.01) = highly significant, *** (p< 0.001) = very highly signifiLCnt compared to diabetic control. † (p<0.05), †† (p<0.01) and ††† (p<0.001) as compared to normal control group.

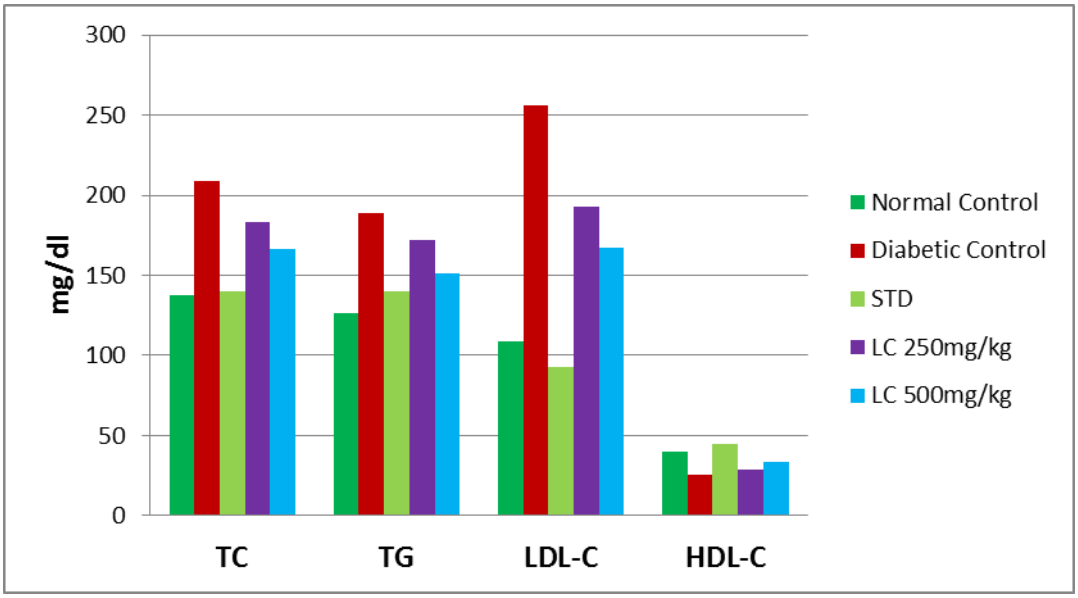

Figure 3: Effect of the ethanolic extract of *L. coromandelica* (LC) on TC, TG, LDL-C and HDL-C level after 21 days feeding in type-2 diabetic rats.

Table 4: Effect of ethanolic extract of *L. coromandelica* (LC) on the serum creatinine level after 21 days feeding in type-2 diabetic rats.

Group	Serum creatinine level (mg/dl)
Normal Control	0.70±0.09
Diabetic Control	2.10±0.20†††
STD (Glibenclamide 10 mg/kg)	0.78±0.09***
LC 250mg/kg	1.67±0.19
LC 500mg/kg	1.14±0.25**

N.B: Data were analyzed by one way ANOVA following Bonferroni post hoc test. Values are expressed as Mean±SEM, n=6. *(p< 0.05) = significant, ** (p< 0.01) = highly significant, *** (p< 0.001) = very highly signifiLCnt compared to diabetic control. † (p<0.05), †† (p<0.01) and ††† (p<0.001) as compared to normal control group.

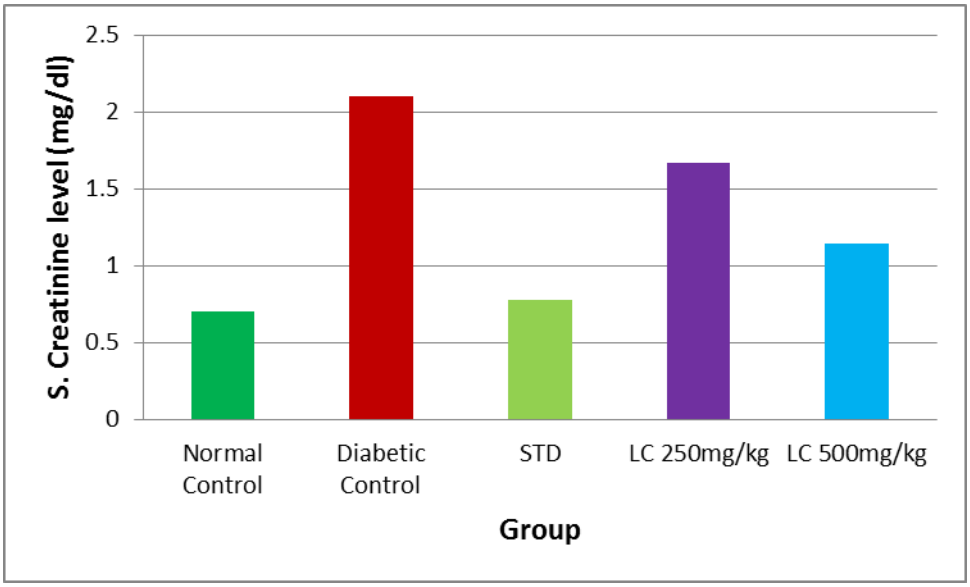

Figure 4: Effect of ethanolic extract of *L. coromandelica* (LC) on the serum creatinine level after 21 days feeding in type-2 diabetic rats.

Table 5: Effect of ethanolic extract of *L. coromandelica* (LC) on the SGPT and SGOT level after 21 days feeding in type-2 diabetic rats.

Group	**ALT** (IU/L)	**AST** (IU/L)
Normal Control	26.83±2.69	47.83±2.32
Diabetic Control	76.67±3.85†††	102.00±4.15††
STD (Glibenclamide 10 mg/kg)	37.33±3.01***	55.00±4.08***
LC 250mg/kg	61.00±3.37*	80.83±4.51**
LC 500mg/kg	48.17±1.92***	62.50±2.55***

N.B: Data were analyzed by one way ANOVA following Bonferroni post hoc test. Values are expressed as Mean±SEM, n=6. *(p< 0.05) = significant, ** (p< 0.01) = highly significant, *** (p< 0.001) = very highly signifiLCnt compared to diabetic control. † (p<0.05), †† (p<0.01) and ††† (p<0.001) as compared to normal control group.

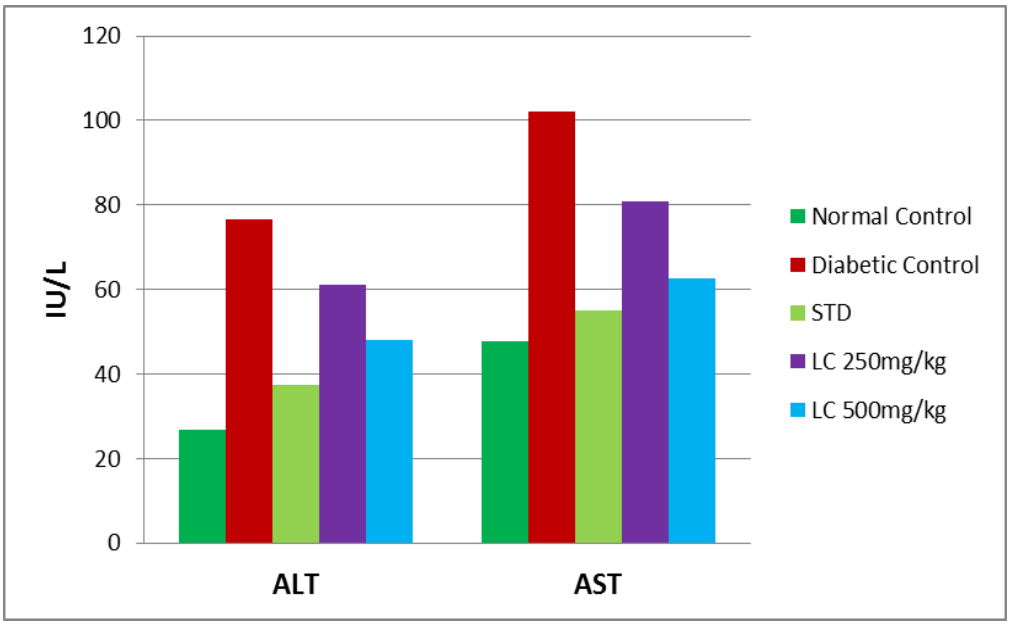

Figure 5: Effect of ethanolic extract of *L. coromandelica* (LC) on the ALT and AST level after 21 days feeding in type-2 diabetic rats.

DISCUSSION

Alloxan has been observed to cause a massive reduction of the β-cells of the islets of Langerhans and induce hyperglycaemia in rats (Ju JB *et. al.,* 2008).

Diabetes mellitus causes disturbances in the uptake of glucose by cells as well as glucose metabolism. Thus, alloxan induced hyperglycemia is a very useful experimental way of studying and demonstrating the activity of new hypoglycemic agents (Srinivasan K and Ramarao P, 2007). Oral glucose tolerance tests were used to analyze blood glucose levels taken at different regular intervals after repeated treatments with *L. coromandelica* bark extracts.

Results of the oral glucose tolerance test, using LC extract indicated remarkable decrease in fasting blood glucose levels of the alloxan induced diabetic rats after 21days. This suggests that the LC extract enhanced glucose utilization and hence improve glucose tolerance in diabetic rats. This also reaffirms that glucose tolerance test (GTT) is a suitable measure and indicator for the cells ability to use glucose, the body's main source of energy (Ali MA *et. al.,* 2015).

The abnormal high concentration of serum lipids is mainly due to increase in the mobilization of free fatty acids from the peripheral fat deposits, because insulin inhibits the hormone sensitive lipase production. The elevated level of serum lipids in DM causes the risk of coronary heart disease (Leite ACR *et. al.,* 2007). However, administering LC to diabetic rats tends to bring the values to near normal. Thus, LC treatments exhibited hypocholesterolaemic and hypotriglyceridaemic effects while at the same time increasing the HDL-C and this may reduce the susceptibility of lipids to oxidation and stabilize the membrane lipids thereby reducing oxidative stress.

Serum creatinine is the most commonly used indicator (but not direct measure) of renal function (Samra M and Abcar AC, 2012). The improvement of creatinine level with the treatment of LC indicated the effect of LC extract on renal function in DM.

In the present study the activities of ALT and AST in serum were altered in DM. In diabetic animals, the changes in the levels of ALT and AST are directly related to changes in metabolism in which the enzymes are involved. The increased activities of transaminases, which are active in the absence of insulin due to the availability of amino acids in the blood of DM and are also responsible for the increased gluconeogenesis and ketogenesis (Gokce G and Haznedaroglu MZ, 2008; Batran SAS, El-Gengaihi SE and Shabrawy OA, 2006). ALT and AST levels also act as an indicator of liver function hence restoration of normal level of these enzymes indicates that the normal functioning of liver (Prince PSM, Menon VP and Pari L, 1997). The restoration of ALT and AST to their respective normal level was observed in the LC treated groups which indicated the ability of the test sample to restore the liver function in diabetic subjects.

CONCLUSION

The overall significance of this study showed that treatment of alloxan-induced diabetic rat, with the extract of *Lannea coromandelica* for 21days, could restore normal bioactivities by shifting to restoring lipid and carbohydrate metabolism homeostasis. Furthermore, LC showed significant renoprotective as well as hepatoprotective actions on alloxan-diabetic rats. On the basis of the above results it can be concluded that *Lannea coromandelica* has significant value as antidiabetic plant and further studies are required to determine the more precise mechanism(s) involved and, to isolate and identify the responsible active compounds.

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