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EFFECTS OF TERMINALIA CHEBULA ON BLOOD BIOCHEMICAL PROFILE AND PANCREATIC TISSUE IN DIABETIC RATS.

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ABSTRACT

The field of herbal medicine has been gaining importance since last many years and many natural products are being used to treat diabetes. Fruit of *Terminalia chebula* has been reported to have anti-diabetic activity. The present study was aimed to evaluate the anti-diabetic effects of aqueous extract of *Terminalia chebula* by evaluating different serological parameters. It was observed that treatment of alloxan-induced diabetic Wistar rats with aqueous extract of *Terminalia chebula* (500 mg/kg body weight) resulted in a significant decrease in blood glucose level. There was no significant increase in serum ALT and AST levels indicating no hepatotoxicity to aqueous extract of *Terminalia chebula.* There was a significant decrease in serum urea and serum creatinine levels upon treatment with aqueous extract of *Terminalia chebula* indicating decreased renal toxicity. Aqueous extract of *Terminalia chebula* induced an improvement in lipid profile values, causing significant decrease in serum cholesterol and serum triglyceride level. In conclusion the present study indicated a significant antidiabetic activity of aqueous extract of *Terminalia chebula* and supported its traditional usage in the control of diabetes and its complications. It can be stated convincingly that use of *Terminalia chebula* alone or in combination of conventional antidiabetic drugs may be beneficial and therefore can reduce the side effects and cost of allopathic treatment for diabetes. However, further studies are needed to evaluate its antidiabetic effects more and its further use as a potential therapy for diabetes.
Keywords: *Terminalia chebula,* Diabetes mellitus, Pancreas,

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases in which there is high blood sugar level due to defects in insulin secretion, or its action, or both. Blood glucose levels are controlled by insulin which is a hormone produced by the pancreas. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia (Sheil 2012). Diabetes is considered as one of the five leading causes of death in the world (Kumar et al. 2008; Sheil 2012). According to World Health Organization projections, the prevalence of diabetes is likely to increase by 35% by the year 2025 (Boyle et al. 2001).

According to Kishore (2012) there are two major types of diabetes i.e type I and type II diabetes. Type I diabetes was formerly called insulin dependent diabetes mellitus (IDDM), in which the pancreas suffers an autoimmune attack by the body itself and becomes incapable to produce insulin. This type of diabetes is commonly seen in juveniles who fail to produce insulin due to destruction of beta-cells of the pancreas (Yallow et al. 1960) and occurs in 10% of diabetics globally (Boyle et al. 2001).

Induction of experimental diabetes in the rats using alloxan is very convenient and simple to use. Alloxan injection leads to the degeneration of beta cells of pancreas. The symptoms of diabetes are clearly seen in rats within 2-4 days following single intraperitoneal injection of 150mg/kg body weight (Lenzen 2012).

Severe stages of acute diabetes can lead to multiple problems including dehydration, weight loss, nausea, vomiting, fatigue, blindness, kidney failure, infections of the bladder and skin. It is also an important factor in accelerating the hardening and narrowing of the arteries (atherosclerosis), leading to strokes, coronary heart disease and other large blood vessel diseases (Kumar et al. 2006).

Hareer (*Terminalia chebula*) is a native plant in South East Asia and is extensively cultivated in Taiwan. It has been reportedly used as laxative, cardiotonic, antidiabetic, anticancer, antimutagenic and antiviral agent (Perry 1980). *Terminalia chebula* promotes digestion, wound healing, ulcer, anemia, swelling and fever. Its fruit is also used as astringent, purgative,

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laxative and gastroprotective (Chatterjee and Pakrasi 2000). Despite known antidiabetic effects of *Terminalia chebula,* detailed studies on various physiological parameters are scarce.

MATERIAL AND METHODS

Animals and Grouping

Fifteen adult healthy Wistar rats, weighing 100-120 g were used for the trial. All the rats used in the study were kept in well ventilated steel cages in the animal shed of University of Veterinary and animal sciences, Lahore throughout the trial. Prior to the study, they were acclimatized for 14 days by keeping them at controlled temperature ranging from 22ºC to 25ºC and relative humidity of 65-70%. They were provided with standard feed and water. A twelve hour light dark cycle was provided artificially to the animals.

After acclimatization the rats were weighed and divided into following three groups containing five rats each and labeled also.

1. Negative control group (A)
2. Positive control diabetic group (B)
3. *Terminalia chebula* treated diabetic group (C)

Dried fruit of *Terminalia chebula* (Hareer) was grinded with the help of pestle and mortar to get a coarse powder. 250 gram of dried powder was suspended in 500 ml of distilled water, mixed well and then kept in incubator at 40ºC for 24 hours. The final yield of extract was then kept in refrigerator to use for the treatment of experimental rats at a daily dose of 500 mg/kg body weight orally for two weeks (Fathy et al. 2012).

Experimental Design

Diabetes was induced in overnight fasted rats of group B and C by a single intraperitoneal injection of Alloxan hydrate (150 mg/kg body weight) prepared in normal saline solution (Szkudelski 2000). Food and water intake was closely monitored after the administration of the drug. The development of hyperglycemia in rats was confirmed 72 hours after alloxan administration, with glucose oxidase method (Carvalho et al. 2003). The animals showing blood glucose level more than 150 mg/dl were considered diabetic and were included in the study.

After Induction, *terminalia chebula* was orally administered to rats of group (C) at a dose of 500 mg/kg body weight once a day in the diet (Fathy et al. 2012).

Blood samples/Serum Collection and Processing

At the end of 14th day, the animals were anesthesized by chloroform. The blood was collected directly from the heart. Whole blood was taken in a covered test tube and labeled. The tube was then centrifuged at 3000 rpm for 10 minutes to separate the serum. The serum was then carefully separated with sterilized pipette into labeled eppendorff tubes. Serum samples were stored at -20˚C for later serological analysis. The samples were maintained at 3-8°C while handling.

Statistical Analysis: The arithmetic means ± SE of biochemical parameters in different groups were calculated. The data were processed on computer software package Statistical package for social sciences version 13. One-way Analysis of Variance was applied to evaluate mean differences in treatment groups. Differences in the means of the group were further analyzed using Post hoc test of LSD. Difference among the means of groups with $p < 0.05$ was considered as significant.

RESULTS

Effect of *Terminalia chebula* on Body weight in alloxan-induced diabetic rats.

The results of Body weights between the different groups i.e. negative control, positive control and treatment group showed that there was no significant difference between any of the groups. The results are shown in Figure 1.

Effect of *Terminalia chebula* on Blood Glucose in alloxan-induced diabetic rats.

The present study showed that values of Blood glucose level of Alloxan induced diabetic group increased significantly (240 ± 7.1 mg/dl) as compared to negative control and treatment group (132 ± 2.5 mg/dl, 132 ± 3.4 mg/dl) respectively. There was no significant difference between Blood glucose levels of negative control rats and terminalia chebula treated diabetic rats. The results are shown in Figure 2.

Effect of *Terminalia chebula* on Biochemical profile in alloxan-induced diabetic rats.

Comparison of serum ALT values between different groups of rats showed that there was no significant difference between values of positive control group and treatment group (60 ± 1.7 mg/dl, 56.2 ± 1.4 mg/dl) respectively. However there was significant decrease (47 ± 3.1 mg/dl) in serum ALT values of negative control group as compared to positive control and treatment group. The results are shown in Figure 3.

Effect of Terminalia chebula on alloxan induced diabetic rats showed that there was no significant difference of serum AST values between any of the groups i.e negative, positive and treatment groups. The results are shown in Figure 4.

In the present study comparison of serum urea values between different rats showed that there was significant difference in values between different groups i.e negative, positive and treatment groups (40 ± 1.7 mg/dl, 89 ± 1.7 mg/dl, 54.4 ± 2.1 mg/dl) respectively. The values of positive control group showed significant increase as compared to negative control or treatment group. The results are shown in Figure 5.

In the present study comparison of serum creatinine values between different rats showed that there was no significant difference in values between negative control and treatment groups (0.55 ± 0.02 mg/dl , 0.65 ± 0.05 mg/dl) respectively. However there was significant increase in serum creatinine values of positive control diabetic group (0.91 ± 0.01 mg/dl) as compared to negative control and treatment groups. The results are shown in Figure 6.

The results of values of serum cholesterol levels between different groups of rats showed that there was significant difference in values between all the groups i.e. negative, positive and treatment groups (103.6 ± 5 mg/dl, 262.6 ± 7.6 mg/dl, 142 ± 6.4 mg/dl). There was significant increase in values of positive control group as compared to treatment and negative control group. The results are shown in Figure 7. Comparison of values in serum triglyceride levels between different groups of rats showed that there was significant difference in values between all the groups i.e negative, positive and treatment groups (105.4 ± 3.4 mg/dl, 179.6 ± 6.4 mg/dl, 137 ± 8.2 mg/dl) respectively. There was a significant increase in values of serum triglyceride in positive control group as compared to negative and treatment group. The results are shown in Figure 8.

DISCUSSION

Body weight

The results of the current study revealed that upon induction of diabetes there was significant decrease of body weight, which is in accordance with the results of Kumar et al. (2006) and Subramanian et al. (2008). It was further concluded that upon administration of aqueous extract of *Terminalia chebula* for 14 days caused significant increase in body weight as compared to negative control group (Kumar et al. 2006).

Blood Glucose Level

The present study showed that there was significant increase in blood glucose level upon induction of diabetes by alloxan, which is in accordance with the findings of Fathy et al. 2012; Kumar et al. 2006; Subramanian et al. 2008; Rao and Nammi. 2006. It was further found that upon administration of aqueous extract of *Terminalia chebula* for 14 days caused significant decrease in blood glucose level as compared to the alloxan induced diabetic group (Fathy et al. 2012; kumar et al. 2006). Such results are also in agreement with those of Murali et al. 2007 and Lee et al. 2010 who evaluated the antihyperglycemic effects of *Terminalia chebula* on various parameters.

Biochemical Profile

Further investigations on various biochemical parameters on blood serum of rats revealed following interesting interpretations.

The serum activities of hepatic enzymes AST and ALT indicate hepatotoxicity and are used as biomarkers for acute early hepatic damage. Results of present study showed that there was insignificant increase in serum AST levels of all groups under treatment. This is in accordance with the results interpreted by Fathy et al. 2012; kumar et al.2006 and Murali et al. 2007 while contrary to the results of Osman and Abbas. 2010 who found an increase in AST activity suggesting that alloxan dose might have hepatotoxic effect.

Investigations on ALT activity indicate that there was insignificant increase in ALT levels of all the groups. These results are in agreement with the results of Murali et al. 2007 who showed that there was no change in liver function while they are contrary to the findings of Fathy et al. 2012 and Osman and Abbas.

2010 who inferred that there was significant increase in ALT activity.

Our studies further investigated the effects of alloxan and *Terminalia chebula* on renal profile of rats. It was found that there was significant increase in values of serum urea upon induction of diabetes by alloxan in rats. These results are in agreement with the findings of Fathy et al. 2012, Osman and Abbas. 2010 and Demerdash et al. 2005 who also said that there is elevation of serum urea level upon induction of diabetes by alloxan while in disagreement with the findings of Murali et al. 2007 and Lee et al. 2010 who said that there is no effect on the serum urea level on the kidney functions. Upon treatment with aqueous extract of *Terminalia chebula* it was revealed that there was significant decrease in elevated levels of serum urea in treatment group. These findings are in contrary to results of Fathy et al.2012 who said that there was no change in levels of elevated serum urea level upon treatment.

The results of serum creatinine level revealed that there was a sharp increase in serum creatinine value upon induction of diabetes. These results are in agreement with Fathy et al. 2012, Osman and Abbas 2010 while contrary to the findings of Murali et al. 2007 who said that there was no effect on renal function upon induction of diabetes. Upon treatment with aqueous extract of *Terminalia chebula* it was revealed that there was significant decrease in elevated levels of serum creatinine in treatment group. These findings are in contrary to results of Fathy et al. 2012 who said that there was no change in levels of elevated serum creatinine level upon treatment.

Diabetes mellitus is associated with hyper lipidemia. Results of our trial showed that there was significant increase in serum cholesterol level upon induction of diabetes with alloxan in rats. These results are in accordance with the results of Fathy et al. 2012 and Osman and Abbas. 2010 who reported marked increase in level of serum cholesterol upon administration of alloxan. Upon treatment with aqueous extract of *Terminalia chebula* there was significant decrease in elevated levels of serum cholesterol which is in accordance with the findings of Fathy et al.2012 who pointed that elevated levels decrease upon treatment.

Results of our trial showed that there was significant increase in serum Triglyceride level upon induction of diabetes with alloxan in rats. These results are in accordance with the results of Fathy et al. 2012 and Osman and Abbas. 2010 who reported marked increase in level of serum Triglyceride upon administration of alloxan. Upon treatment with aqueous extract of *Terminalia chebula* there was significant decrease in elevated levels of serum Triglyceride which is in accordance with the findings of Fathy et al.2012 who pointed that elevated levels decrease.

RESULTS

4.1. Effect of *Terminalia chebula* on Body weight in alloxan-induced diabetic rats.

The results of Body weights between the different groups i.e. negative control, positive control and treatment group showed that there was no significant difference between any of the groups. The results are shown in Figure 1.

4.2. Effect of *Terminalia chebula* on Blood Glucose in alloxan-induced diabetic rats.

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4.3. Effect of *Terminalia chebula* on Biochemical profile in alloxan-induced diabetic rats.

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Effect of Terminalia chebula on alloxan induced diabetic rats showed that there was no significant difference of serum AST values between any of the groups i.e negative, positive and treatment groups. The results are shown in Figure 4.

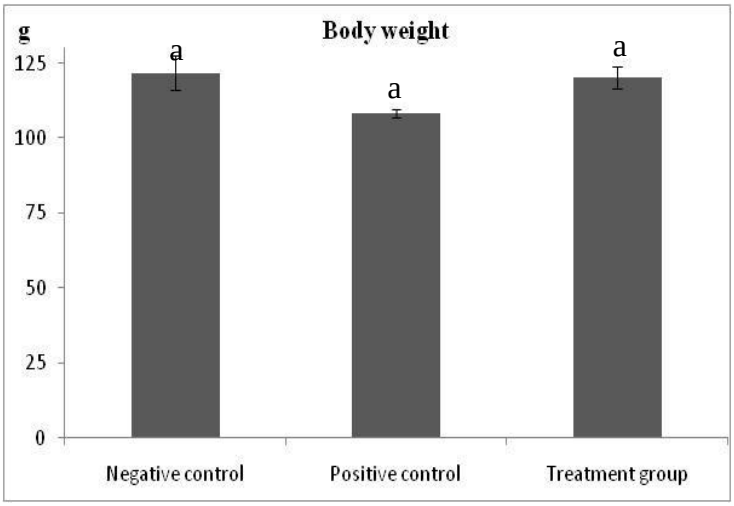

Figure 1. Effect of *Terminalia chebula* on body weight in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

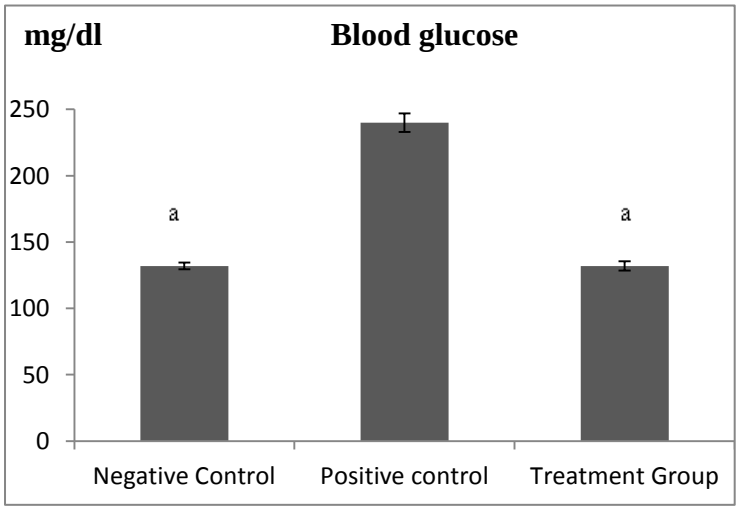

Figure 2. Effect of *Terminalia chebula* on Blood glucose in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

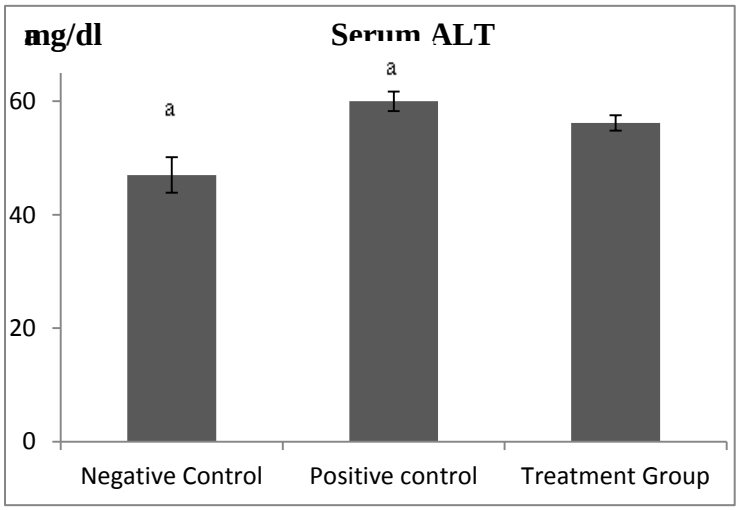

Figure 3. Effect of *Terminalia chebula* on serum ALT in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

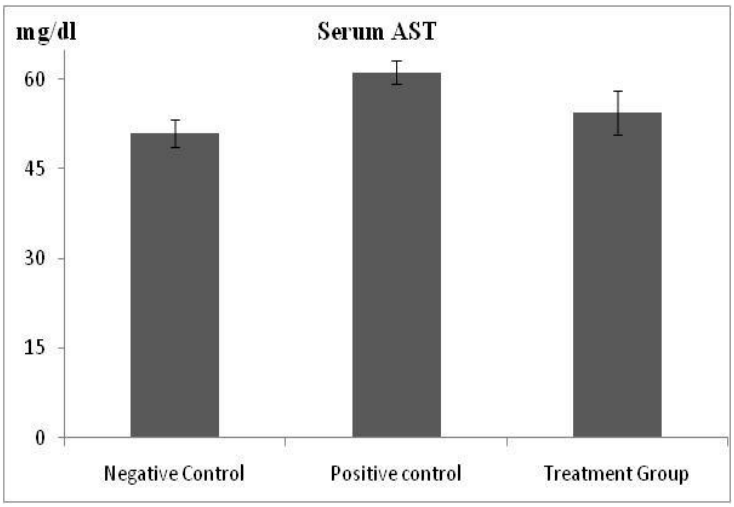

Figure 4. Effect of *Terminalia chebula* on serum AST in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

In the present study comparison of serum urea values between different rats showed that there was significant difference in values between different groups i.e negative, positive and treatment groups (40 ± 1.7 mg/dl, 89 ± 1.7 mg/dl, 54.4 ± 2.1 mg/dl) respectively. The values of positive control group showed significant increase as compared to negative control or treatment group. The results are shown in Figure 5.

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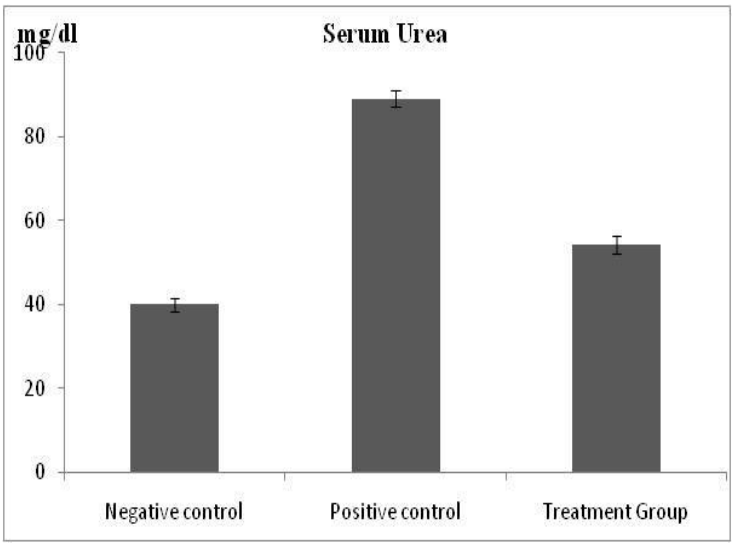

Figure 5. Effect of *Terminalia chebula* on serum urea in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

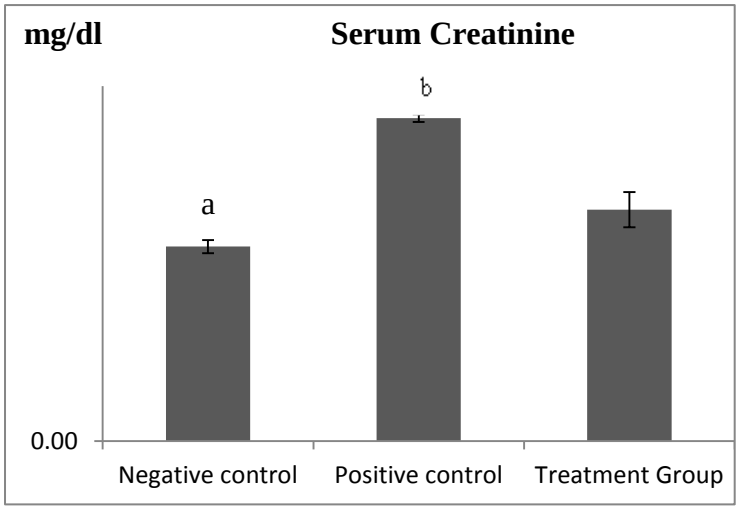

Figure 6. Effect of *Terminalia chebula* on serum creatinine in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

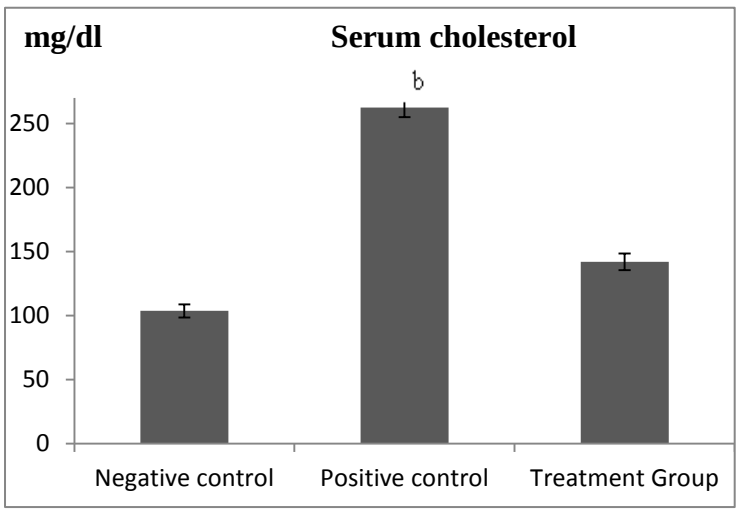

Figure 7. Effect of *Terminalia chebula* on serum cholesterol in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

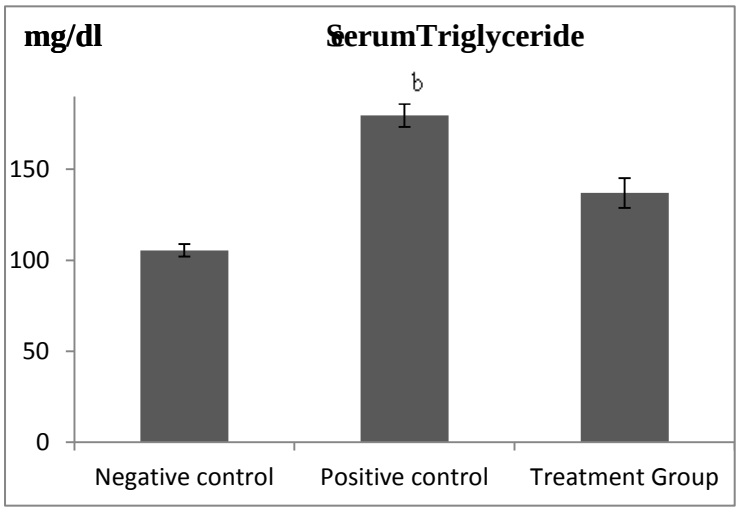

Figure 8. Effect of *Terminalia chebula* on serum Triglyceride in alloxan-induced diabetic rats. Data was presented as mean ± SEM. Values with different letters represent significant difference.

4.4. Histological Study of Pancreatic Tissue

Histological studies on Pancreatic tissues of normal rats revealed that there were normal islets and no hyaline and necrotic changes and average diameter of islets of Langerhans was normal. The results are shown in Figure 9.

Histological studies on Pancreatic tissues of diabetic rats showed that there were shrunken islets of Langerhans showing hyaline and necrotic changes. The islet cells were small and oval in shape with necrotic changes. The results are shown in Figure 10.

Histological studies on Pancreatic tissues of diabetic rats treated with *Terminalia chebula* showed that the islet cells appeared spherical in shape and larger in size and displayed increase in size and light hyaline changes in the majority of cells after 14 days of treatment. The islets of Langerhans in treated groups were showing slight increase in size and hyaline changes in the majority of cells. The results are shown in Figure 11.

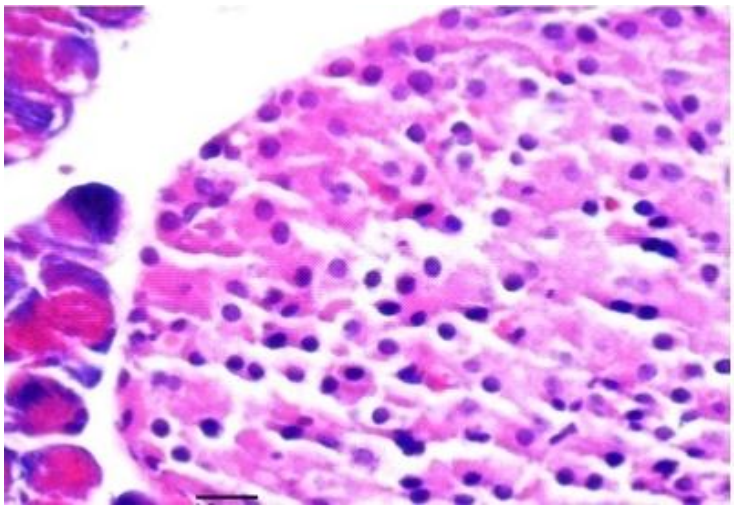

Figure 9. Photomicrograph of rat's pancreatic Islet of Langerhans (H and E. ×80). Normal Controlled rats with normal islets and no hyaline and necrotic changes and average diameter of islets of Langerhans was normal.

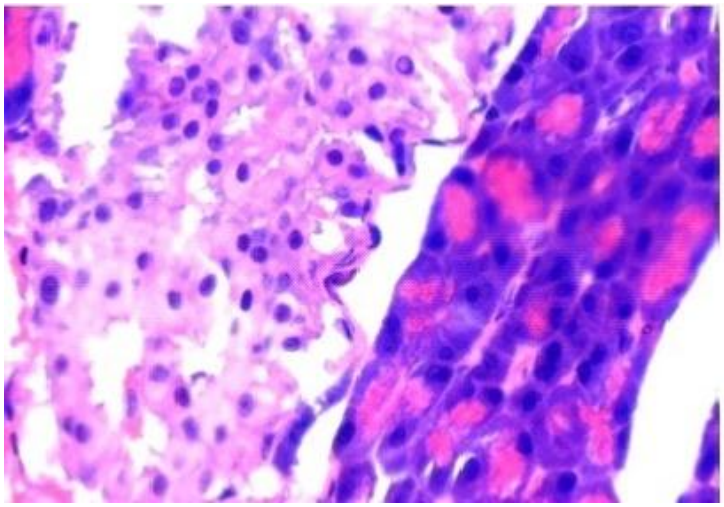

Figure 10. Photomicrograph of rat's pancreatic Islet of Langerhans (H and E. ×80). Diabetic Controlled rats with shrunken islets of Langerhans showed hyaline and necrotic changes. The islet cells were small and oval in shape with necrotic changes.

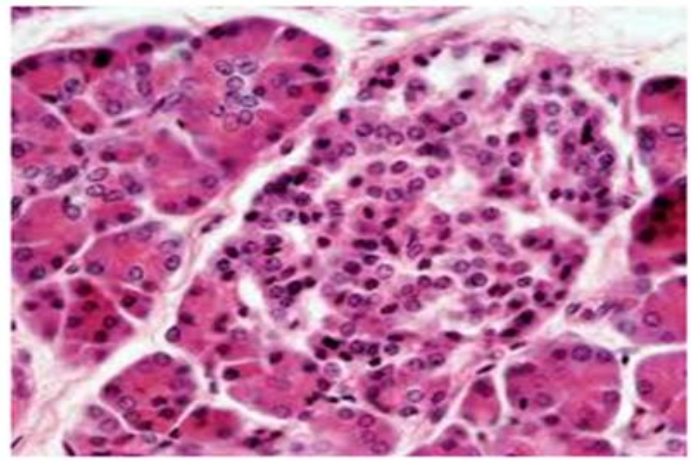

Figure 11. Photomicrograph of rat's pancreatic Islet of Langerhans (H and E. ×80). In Diabetic treated group with *Terminalia chebula* rats, the islet cells appeared in spherical shaped and larger in size and displayed increase in size and light hyaline changes in the majority of cells after 14 days of treatment. The islets of Langerhans in treated groups are showing slight increase in size and hyaline changes in the majority of cells.

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