

Antidiabetic and hepatoprotective activities of *Tamarindus indica* fruit pulp in alloxan induced diabetic rats

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ABSTRACT

Background: *Tamarindus indica* belongs to family Caesalpiniaceae. Fruit pulp of *Tamarindus indica* is believed to have antidiabetic, hepatoprotective and many other medicinal properties. The objective of this study was to investigate antidiabetic, hypolipidemic and hepatoprotective activity of ethanolic extract of *Tamarindus indica* fruit pulp in alloxan induced diabetic rats.

Materials and Methods: Animals were divided into 5 groups (n = 6). Normal and diabetic control groups received normal saline and alloxan (150 mg/kg body weight intraperitoneally) respectively. Animals were made diabetic by injection of single dose of alloxan in three test groups and after that they were treated with ethanolic extract of fruit pulp of *Tamarindus indica* 300 and 500 mg/kg/body weight orally and metformin 150 mg/kg body weight orally respectively for 14 days. Antidiabetic activity was estimated by measuring serum glucose and lipid profile; and hepatoprotective activity was measured by estimating serum liver enzyme levels and histopathological changes in liver tissues. Results were analyzed by One way ANOVA followed by Scheffe multiple comparison tests (p<0.01).

Results: The two dose levels of *Tamarindus indica* significantly altered alloxan induced changes in serum glucose, lipid profile and serum enzyme levels. But in liver histopathology, higher dose (500 mg/kg) of plant showed complete regeneration whereas lower dose (300 mg/kg) showed only partial improvement in liver histopathology profile.

Conclusion: Present study revealed that *Tamarindus indica* possesses antidiabetic and hepatoprotective activity in alloxan induced diabetic rats.

Key words: *Tamarindus indica*, alloxan, antidiabetic, hepatoprotection

Citation: Koyaguru N, Kumar VH, Jamadar MG, Huligol SV, Nayak N, Yendigeri SM, et al. Antidiabetic and hepatoprotective activities of *Tamarindus indica* fruit pulp in alloxan induced diabetic rats. Int J Pharmacol and Clin Sci 2013;2:33-40.

INTRODUCTION

Diabetes mellitus is an endocrine disorder which mainly alters blood glucose levels. An altered blood glucose level mainly is due to defect in insulin secretion, insulin action or both.^[1] In addition, hyperlipidemia is also induced by the secondary effect of diabetes. It was well documented that rise in blood lipids levels is major risk factor for cardiovascular disorders.^[2]

Although many of the drugs are available in the market, none of them are proved to

be promising agents to cure diabetes completely. As alternative approaches for the treatment of diabetes are urgently needed, various traditional plants have been used in the treatment of diabetes. In the present study, we attempted to get the reliable data of a herbal to be effective in the treatment of diabetes and hepatotoxicity.

Received : 06 - 05 - 2013

Revised : 26 - 07 - 2013

Accepted : 03 - 08 - 2013

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Conflict of interest: Nil

Source of support : Nil

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Liver is the most important organ, which plays a pivotal role in regulating various physiological processes in the body. It is involved in several vital functions, such as metabolism, secretion and storage and also detoxification and synthesizes useful principles.^[3] Liver diseases are mainly caused by toxic chemicals, excess consumption of alcohol, infections and autoimmune disorders.^[4] Hepatotoxic agents cause structural abnormality in the liver which alters normal physiological functions of this organ.

Alloxan is economical to induce Diabetes mellitus to screen antidiabetic herbals in experimental animals. It has been shown to produce diabetes by damaging islet cells of pancreas by liberating oxygen radicals. These free radicals are also involved in the other tissue damage (liver and kidney etc.) which occurs in the progression of DM.^[5, 6]

Tamarindus indica Linn. (family: Caesalpinaceae) is known as tamarind, a well known plant of the Indian medicinal system. This plant possesses antidiabetic, hypolipidemic, hepatoprotective, antioxidant, antifungal, anti-inflammatory, antimalarial and antibacterial activities and antiparasitic toxicity.^[7,8] The fruit pulp has been reported to contain ascorbic acid, β -carotene, tartaric acid, lactic acid, citric acid, and maleic acid which are responsible for hepatoprotective activity. Pulp of fruits has antidiabetic, hypolipidemic, antioxidant and hepatoregenerative activities.^[9,10]

According to review of literature, alloxan has been shown to produce diabetes mellitus. In addition to this, it also causes damage to liver parenchyma on progression of diabetes mellitus. Seeds and leaves of *Tamarindus indica* are already reported to have antidiabetic property but there is inadequate data on *Tamarindus indica* fruit pulp though it is reported to have hypoglycemic activity.^[11,12] There is lack of literature on antidiabetic and

hepatoprotective activities of fruit pulp of *Tamarindus indica* in alloxan model. Hence, the present study was undertaken to investigate antidiabetic, hypolipidemic and hepatoprotective activity of ethanolic extract of *Tamarindus indica* fruit pulp in alloxan induced diabetic rats.

MATERIALS AND METHODS

Experimental animals

Male Wistar albino rats weighing between 180 – 250 gms were obtained from animal house, Al-Ameen Medical College, Bijapur, India. Rats were housed in polypropylene cages (UN Shah Manufacturers, Mumbai) and provided with standard pellet food (Hindustan lever ltd, Mumbai, India). Animals were maintained at a room temperature of $(23 \pm 2)^{\circ}\text{C}$, with a fixed 12-h light: dark cycles and humidity $50 \pm 5\%$. The experimental protocol was approved by local Institutional Animal Ethical Committee of Al-Ameen Medical College, Bijapur, India.

Drugs and chemicals

Alloxan was procured from Explicit Chemicals private limited, Pune, India. Metformin was obtained from USV Limited, Mumbai, India. Ketamine injection was obtained from Neom laboratories limited, Mumbai, India. The biochemical parameters were measured by using commercially available kits (Erba Mannheim, Transasia Biomedicals LTD.)

Collection of plant material

The fruit pulp of *Tamarindus indica* was purchased from local market in Bijapur, Karnataka, India and was authenticated from Department of Botany, BLDEA University, Bijapur, Karnataka, India.

Preparation of plant extract

Fresh fruits of *Tamarindus indica* were cut into small pieces, seeds were removed

and air dried. The dried pieces of *Tamarindus indica* fruit pulp, weighing 100 g, were soaked in 500 ml of 95% ethanol in a round flask for about 24 hours. The process of extraction was done by reflux condensation method using soxhlet apparatus at 60-80 °C for 9 hours. The extract was concentrated by distillation apparatus till a syrupy consistency was obtained. Finally, the extract was put in a china dish and evaporated at 40-60 °C temperature in a water bath. 22 gms of semisolid extract was obtained.^[13]

Acute toxicity study

This study was performed to select optimum doses to evaluate the antidiabetic and hepatoprotective properties of *Tamarindus indica* fruit pulp.

Albino wistar rats of either sex weighing 180-250 gms were divided into four groups (n = 2). They were fasted overnight before administration of extract. They were administered ethanolic extract of *Tamarindus indica* fruit pulp orally in a single increasing doses of 100, 300, 1000 and 3000 mg/kg body weight respectively. The animals were observed continuously for first 2 hrs and then occasionally for 4 hrs for any gross change in behavioral, locomotor activity or any other symptoms of toxicity and finally for overnight mortality. The dose, upto 3000 mg/kg, was well tolerated without producing any changes in gross behavior, signs of toxicity and mortality. Hence, the dose selected for the study was 10% of the maximum tolerated dose, 300 mg/kg body weight orally and subsequently another higher dose 500 mg/kg body weight was selected for administration to the rats.^[14,15]

Experimental induction of diabetes

Diabetes was induced by injecting alloxan (150 mg/kg body weight intra peritoneally) in normal saline, after baseline glucose estimation was done.^[16] After one hour of

alloxan injection animals were allowed food and water *ad libitum*. The diabetes was assessed in alloxan-induced rats by determining the blood glucose concentration, 3 days after injection of alloxan. The rats with fasting blood glucose level above 260 mg/dl were selected for the experimental study.

Study design

Thirty healthy male albino rats were divided into 5 groups, each containing 6 rats. The experimental groups were as follows: Group 1 (control animals) received gum acacia 2% orally. Group 2, 3, 4 and 5 animals were treated with alloxan (150 mg/kg bodyweight, intra peritoneal) to induce diabetes mellitus. Group 2 which was considered as diabetic control received gum acacia 2% orally. But groups 3, 4 and 5 animals were treated with standard drug (metformin 150 mg/kg oral), 300 and 500 mg/kg bodyweight ethanolic extract of *Tamarindus indica* fruit pulp oral respectively.

After induction of diabetes with alloxan, the diabetic rats were treated with plant extract and standard drug orally once daily for 14 days. After completion of 14 days of treatment, blood was collected by retro-orbital puncture and serum was separated by using centrifugation at 4000 rpm for 10 minutes.

The animals were sacrificed on 14th day of treatment by injecting high dose of ketamine anaesthesia and liver tissues were removed.^[15-17] The liver tissues were washed thoroughly with normal saline and fixed in 10% formalin, dehydrated in alcohol and then embedded in paraffin. 5µm thick sections from each liver samples were made and stained with haematoxylin- eosin dye for the microscopic observations of the liver architecture.

Biochemical estimation

All biochemical estimations were done by using fully automated analyzer (ERBA-EM 200).

For serum glucose estimation glucose oxidase and peroxidase (GOD-POD) method, for triglycerides Glycerol Phosphate Oxidase-peroxidase (GPO-POD), for total cholesterol, HDL and LDL, Cholesterol Oxidase-Peroxidase (CHOD-PAP) methods were employed. VLDL was estimated using the formula, $VLDL = \text{triglycerides} / 5$.

For estimation of serum Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP), kinetic- IFCC method was used and for Aspartate aminotransferase (AST) IFCC without pyridoxal phosphate method was used.

Histopathology

A small portion of liver was fixed in 10% formalin solution for histopathological studies. Liver sections were made 5 μ m thick, and stained with hemotoxylin and eosin (H&E) stain. After staining, the sections were observed under an electronic microscope at 45X and photographs were taken.

Statistical analysis

The data was represented as Mean \pm SEM. Results were analyzed by one-way ANOVA followed by Scheffe multiple comparison tests using SPSS software. The minimum level of significance was set at $p < 0.01$.

RESULTS

Serum glucose

After 3 days of administration of alloxan, a significant increase in fasting blood glucose levels compared with the normal control (Group 1) was observed in groups 2, 3, 4 and 5. Antidiabetic effect of *Tamarindus indica* extract (300 and 500 mg/kg) and metformin was found statistically significant ($p < 0.01$) when compared to alloxan treatment group (Table 1).

Lipid profile

There was a significant increase in cholesterol, LDL, VLDL and TGs and decrease in HDL levels in alloxan treated rats in comparison to control group. Treatment to diabetic rats with ethanolic extract of *Tamarindus indica* (300 and 500 mg/kg) and metformin significantly ($p < 0.01$) decreased the elevated cholesterol, LDL, VLDL and TGs and significantly increased HDL levels (Table 1).

Liver enzymes levels

Administration of alloxan significantly increased serum AST, ALT and ALP levels in comparison to control group showing alloxan induced hepatotoxicity. There was a significant ($p < 0.01$) reduction of the elevated liver enzyme

Table 1: Effect of ethanolic extract of *Tamarindus indica* fruit pulp on blood glucose and lipid profile in alloxan induced diabetic rats.

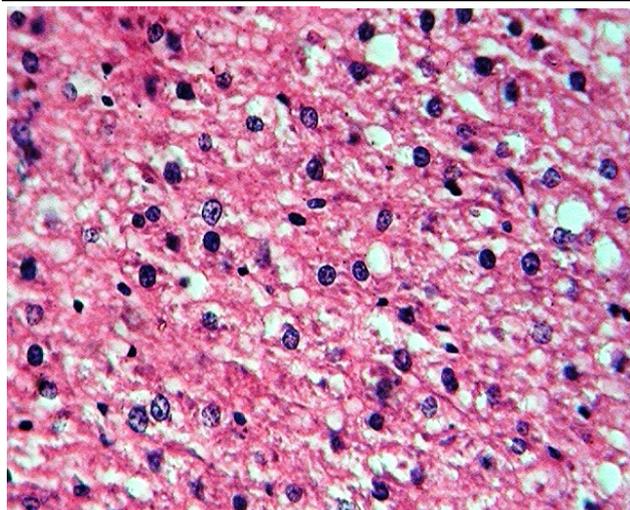
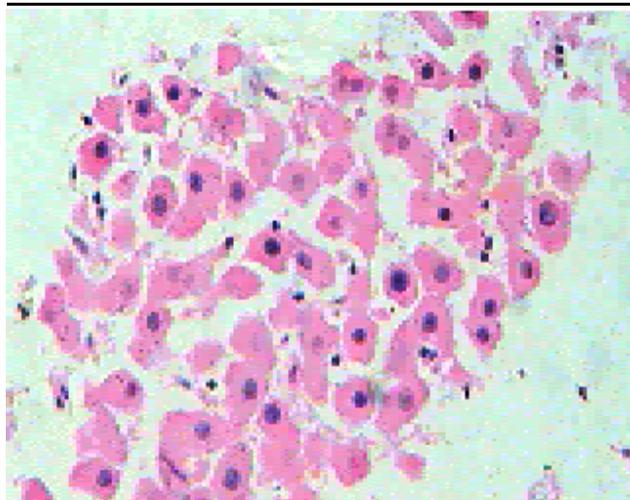
Group (n=6)	Glucose (mg/dl)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal control	108.94 \pm 1.81	112.62 \pm 2.7	99.19 \pm 3.17	49.68 \pm 2.77	36.28 \pm 1.53	18.92 \pm 1.19
Diabetic control	378.74 \pm 0.92*	191.75 \pm 1.69*	176.85 \pm 2.48*	15.73 \pm 0.87*	95.02 \pm 1.76*	34.29 \pm 2.42*
<i>T. indica</i> extract (300 mg/kg)	188.6 \pm 2.67 [†]	146.55 \pm 1.39 [†]	135.49 \pm 1.53 [†]	32.74 \pm 0.62 [†]	46.79 \pm 1.06 [†]	26.14 \pm 0.73 [†]
<i>T. indica</i> extract (500 mg/kg)	179.59 \pm 2.01 [†]	130.47 \pm 1.05 [†]	118.45 \pm 1.03 [†]	37.36 \pm 0.96 [†]	43.11 \pm 1.05 [†]	22.89 \pm 0.74 [†]
Metformin (150 mg/kg)	165.98 \pm 0.76 [†]	150.87 \pm 2.72 [†]	131.6 \pm 1.71 [†]	27.02 \pm 1.9 [†]	49.59 \pm 2.18 [†]	26.05 \pm 1.08 [†]

Values are expressed in mean \pm SEM, * $p < 0.01$ vs. normal control, [†] $p < 0.01$ vs. diabetic control

Table 2: Effect of ethanolic extract of *Tamarindus indica* fruit pulp on liver enzyme levels in alloxan induced diabetic rats

Group (n=6)	ALT (IU/L)	AST (IU/L)	ALP (IU/L)
Normal control	47.31 ± 1.78	64.75 ± 1.47	104.25 ± 3.46
Diabetic control	100.23 ± 1.76*	112.29 ± 2.29*	152.31 ± 2.31*
<i>T. indica</i> extract (300 mg/kg)	74.26 ± 2.03 [†]	88.06 ± 2.62 [†]	133.02 ± 1.79 [†]
<i>T. indica</i> extract (500 mg/kg)	55.05 ± 1.38 [†]	70.55 ± 1.49 [†]	109.19 ± 3.44 [†]
Metformin (150 mg/kg)	71.24 ± 2.05 [†]	82.79 ± 1.33 [†]	130.82 ± 2.22 [†]

Values are expressed in mean ± SEM, *p < 0.01 vs. normal control, [†]p < 0.01 vs. diabetic control

Figure 1: Rat liver treated with gum acacia with normal hepatic architecture (45X)**Figure 2: Alloxan induced hepatic degeneration and necrosis of hepatocytes (45X)**

levels in diabetic rats treated with either ethanolic extract of *Tamarindus indica* or metformin (Table 2).

Histopathological examination

Treatment with alloxan caused central vein congestion, increased size of hepatocytes, ballooning degeneration and necrosis of hepatocytes in comparison to control group (Figure 1, 2). However, treatment with metformin (Figure 3) and *Tamarindus indica* extract 500 mg (Figure 4) restored the pathological changes induced by alloxan. But, in the treatment with 300 mg dose (Figure 5) of *Tamarindus indica* extract showed only partial improvement in the cytoarchitecture of the liver.

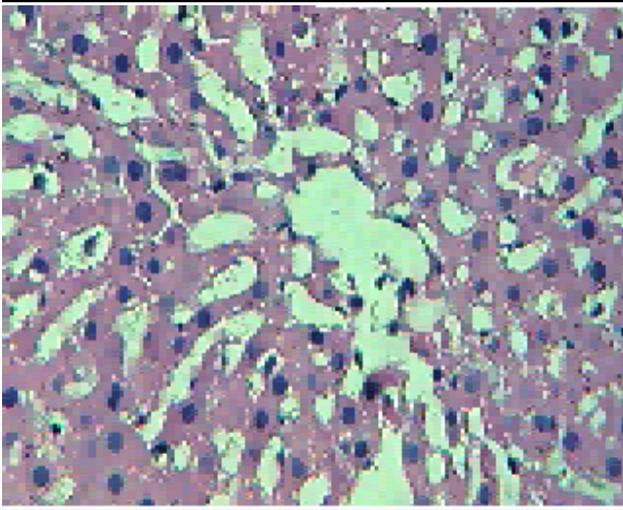
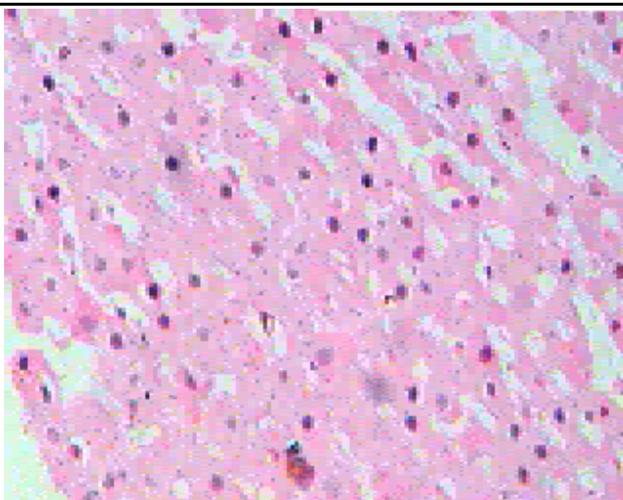
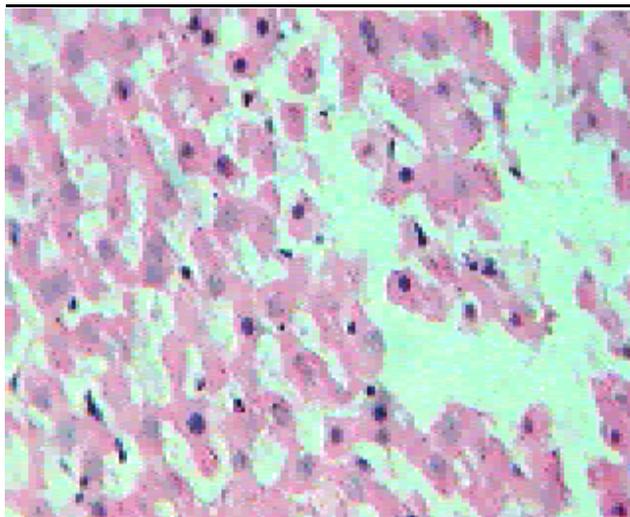
Figure 3: Alloxan and metformin shows normal cytoarchitecture of liver with visible central veins (45X)**Figure 4: Alloxan and *T. indica* 500mg/kg shows normal cytoarchitecture of liver with visible central veins (45X)**

Figure 5: Alloxan and *T. indica* 300 mg/kg with partial improvement in cytoarchitecture of liver (45X)



DISCUSSION

Treatment with ethanolic extract of *Tamarindus indica* fruit pulp (300 and 500 mg/kg) has effectively reduced serum glucose, lipid levels and hepatic markers in alloxan treated rats. In histopathological examination of liver, metformin and 500 mg/kg of *Tamarindus indica* fruit extract showed significant improvement in liver pathology induced by alloxan. However, 300 mg/kg *Tamarindus indica* fruit extract failed to regenerate the liver parenchyma to the normal level.

In the present study, alloxan treatment showed a significant elevation in glucose and lipid levels i.e., cholesterol, TG, LDL and VLDL and a reduction in HDL and also reported that elevation of hepatic markers i.e., AST, ALT and ALP levels. The possible mechanism might be that free radical generation by the alloxan causes damage to β -cells of pancreas, leading to insulin deficiency which results in hyperglycemia and also associated with hyperlipidemia.^[18] The mechanism of alloxan induced hepatotoxicity could be attributed to decrease in antioxidant enzymes, accompanied by a significant increase in aldehyde products of lipid peroxidation, leading to hepatic oxidative stress in rats.^[19]

Our study revealed that oral administration of *Tamarindus indica* extract (300 and 500 mg/kg) significantly decreased blood glucose and lipid levels i.e., total cholesterol, LDL, VLDL and triglycerides, and increased HDL-cholesterol levels in alloxan induced diabetic rats. Antidiabetic activity is supported with the earlier study with methanolic extract of fruits and seeds of *Tamarindus indica* which reduced elevated glucose levels in glucose induced hyperglycemia in mice.^[9] In accordance with this study, the possible mechanism of antidiabetic and hypolipidemic activity of *Tamarindus indica* fruit pulp extract, is mainly due to the presence of polyphenolic compounds (limonene etc.). In addition to this, it also possesses antioxidant property which could be beneficial in diabetes.^[9] Hypolipidemic activity of this plant strongly correlated with other study treated with ethanolic extract of fruit pulp of *tamarindus indica*, significantly reduced lipid levels in cafeteria induced obese rats.^[20]

Several studies have shown that oxidative free radicals generated by alloxan administration being the most common etiology for the destruction of vital organs of the body. Liver is one of the organs damaged by free radicals.^[21] It was evident by present study which has shown that an increase in hepatic marker enzymes i.e. ALT, AST and ALP to the abnormal levels. But, administration of ethanolic extract of *Tamarindus indica* fruit pulp significantly reduced these elevated enzyme levels. The underlying mechanism might be due to the presence of antioxidant polyphenolic components in the fruit which could be beneficial in treatment of liver damage in diabetes.^[9]

The histopathological examination of liver in diabetic rats showed a marked degeneration of the liver parenchyma correlated with other study [22]. Treatment with higher dose of (500 mg/kg) *Tamarindus indica* fruit extract

improved the cytoarchitecture, with visible central veins surrounded by hepatocytes and well arranged hepatic ducts, which indicates that the plant extract possesses hepatoprotective activity.

This study had some limitations. The evaluated of the effect of *Tamarindus indica* fruit extract on pancreas regeneration, viable beta cell count and insulin levels, would have given strong evidence of its antidiabetic activity. The effect of extract on body weight changes, mortality, glucose loading and its tolerance would have generated more evidences.

In conclusion, administration of *Tamarindus indica* fruit extract significantly reduced blood glucose levels in alloxan induced diabetic rats. It also showed hypolipidemia as well as hepatoprotective effects. Further identification

and isolation of active phytochemical constituents of *Tamarindus indica* fruit pulp and their underlying mechanisms responsible for glucose lowering and hepatoprotective activity may be useful in developing a new drug for the treatment of diabetes complications in human beings in near future.

ACKNOWLEDGEMENT

We are sincerely thankful to Dr.M.B.Mullimoni Professor, Department of Botany, BLDEA University for Identification and Authentication of *Tamarindus indica* fruit. We are also thankful to department of Pharmacognosy, BLDEA College of pharmacy for their kind support during extraction procedure. We are also grateful to Explicit chemicals private LTD, Pune for providing alloxan gift sample.

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