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# Antihyperglycemic and hypolipidemic effect of *Morus indica* L. in streptozotocin induced diabetic rats

**D. Vishalakshi Devi and Asna Urooj**

*Department of Studies in Food Science and Nutrition, University of Mysore, Manasagangotri, Mysore-570006, India*

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**Abstract**

The present study evaluated the long term hypoglycemic effect of *Morus indica* L. in rats induced with diabetes, to determine the changes in activity of glycolytic and gluconeogenic enzymes and to compare the effect of *Morus indica* L. with conventional antidiabetic drugs - Insulin and Glibenclamide (OHA). *Morus indica* L. was obtained from the Department of Studies in Sericulture, University of Mysore, India. The antihyperglycemic effect of the plant was tested in streptozotocin induced diabetic rats. The effect of *Morus indica* L. on carbohydrate metabolizing enzymes was also studied. *Morus indica* powder (MIP) at a level of 500mg/kg body weight, reduced blood glucose level in the animals by 42% after 45 days. The blood glucose in animals supplemented with MIP decreased from an initial level of 257± 69.4 to 148.8 ± 34.48 mg/dl. The activity of aldolase in the liver of MIP and Insulin treated groups was 0.19u/g and in Glibenclamide treated group, it was 0.18u/g protein. The activity of G-6-PDH decreased significantly ($p<0.05$) in untreated diabetic group (0.24 ± 0.04 mIU/mg). The G-6-PDH levels in MIP, Insulin and Glibenclamide treated group were 1.38 ± 0.48, 0.98 ± 0.10 and 1.04 ± 0.42 mIU/mg protein, respectively which were higher compared to the diabetic control group. The activities of AsAT and AlAT decreased significantly in animals treated with *Morus*, Insulin and Glibenclimide. The results prove that *Morus* could effectively reduce the blood glucose, total cholesterol, triglycerides and also reverse the activity of elevated enzymes which can prove beneficial in the management of hyperglycemia.

**Key words:** *Morus indica* L., mulberry, aldolase, antihyperglycemic, glucose-6-phosphate dehydrogenase, hypolipidemic

## 1. Introduction

Diabetes mellitus is the most severe metabolic pandemic of 21st century, affecting essential biochemical activities in almost every cell in the body and increasing the risk of cardiac problems (Gupta *et al.*, 2008). Diabetes is possibly the world's fastest growing metabolic disease; it is the third commonest disease in the world next to the cardiovascular and oncological disorders according to World Health Organization data (Srinivasan, 2005).

Though different types of oral hypoglycemic agents are available along with insulin for the treatment of diabetes mellitus, there is increasing demand by patients to use the natural products with antidiabetic activity (Venkatesh, 2003). Clinical examinations have demonstrated hypoglycemic and hypolipidemic activity in extracts from many plants (Kelkar *et al.*, 1996; Ragavan *et al.*, 2006; Kumar *et al*, 2005; Vasanthamani and Savitha, 2001; Chandrashekar *et al.*, 1989; Kaleem *et al.*, 2006).

The relationship between diabetes and hyperlipedemia is a well-recognized phenomena. Hypercholesterolemia is common in diabetes, contributing to the high prevalence of accelerated atherosclerosis and coronary heart disease. Increase in plasma triglycerides and very low density lipoproteins have been found in diabetic patients (Andallu *et al.*, 2001). Several studies have reported increases in the concentration of lipid peroxides in the blood and urine of diabetics, and also considerable changes in the structural organization and functions of red blood cell membrane are seen (Shukla *et al.*, 2000).

Medicinal plants have an important role in modulating glycemic responses and have preventive and therapeutic implications for certain conditions such as diabetes, hyperlipedemia, *etc*. Many Indian medicinal plants have been found to be useful in successfully managing diabetes, significant among them are : *Gymnema sylvestre, Pterocarus marupium, Eugenia jambolana, Swertia chiraita, Syzigium cumini, Momordica charantia, Fenugreek, T. arjuna,* the active principles have been isolated from some of them (Kaleem *et al.*, 2006; Shukla *et al.*, 2000).

The hypoglycemic effect of *Morus indica* L. has been studied in animal model wherein the plant in the dehydrated powder form was supplemented at 25% level in the diet (Shukla *et al.*, 2000). This amount is practically not feasible for consumption, also there are no detailed studies on the effects of *Morus indica* L. on the biochemical parameters and activity of enzymes abnormally altered due to diabetes mellitus. The results of a preliminary study wherein *Morus indica* powder was supplemented at a level of 500mg/kg

**Author for correspondence:** Professor Asna Urooj
*Department of Studies in Food Science and Nutrition,University of Mysore, Manasagangotri, Mysore-570006, Karnataka, India*
**E-mail:** asnau321@gmail.com
**Tel.:** +91-09448489334; Telefax: +91 821 2419632

body weight reduced the blood glucose of diabetic rats (Vishalakshi and Urooj, 2008). With this background, the present study was planned to evaluate the long term hypoglycemic effect of *Morus indica* L. in rats induced with diabetes. In addition, the changes in activity of glycolytic and gluconeogenic enzymes was also determined and compared with conventional antidiabetic drugs Insulin and Glibenclamide (OHA).

## 2. Materials and Methods

### 2.1 Materials

Fresh Mulberry leaves (*Morus indica* L. MIP) were obtained from the Department of Studies in Sericulture, University of Mysore, India and subsequently identified by a botanist, DOS in Botany, University of Mysore, Mysore. The leaves were washed, oven dried (55-60°C), ground, passed through sieve and stored in airtight container at refrigeration temperature before use.

Streptozotocin was procured from Sigma chemicals, Bangalore. GOD-POD kit from Span Diagnostics (Surat, India). Glucose-6-phosphate dehydrogenase (G-6-P) and Aldolase kits from Randox Laboratories Ltd. Worli, Mumbai. Glutamic oxaloacetic transaminase (AsAT) and Glutamic pyruvate transaminase (AlAT) kits from Aggappe Diagnostics Ltd, Kerala. Total cholesterol, Triglycerides kits from Coral clinical systems, Verna, Goa. Tris (hydroxymethyl) aminomethane from SD Fine Chemicals, Bombay. All the other chemicals used were of analytical grade and purchased locally.

Male albino rats (30) of Wister strain with body weights ranging from 150-200g were procured from Central Animal House, Department of Zoology, University of Mysore. The study was approved by the Institutional Animal Ethics Committee, University of Mysore (No.MGZ/578/2005-06). The animals were housed in individual cages and were allowed to acclimatize for 15 days with cereal-pulse based diet which consisted of wheat flour (62%), defatted soya flour (18%), groundnut oil (10%), sugar (7%), vitamin mix (1%) and mineral mix (2%) and water was provided *ad libitum*.

### 2.2 Experimental design

(a) The animals were divided into five groups (n=6) based on their weights, using Randomized block design which is as follows: Group I-Normal control (NC), Group II - Diabetic control (DC), Group III-Diabetic group treated with *Morus indica* (MIP), Group IV-Diabetic group treated with Insulin (INS), Group V-Diabetic group treated with Glibenclamide (GNB).

(b) Animals of group II, III, IV and V were rendered diabetic by a single i.p injection of Streptozotocin (STZ) (55mg/kg b.wt) (Andallu and Varadacharyulu, 2003) prepared in freshly prepared 0.1M citrate buffer after an overnight fast. The diabetic animals were provided 5% glucose solution for 24 h following Streptozotocin injection to prevent initial drug-induced hypoglycemic mortality. After 72 h of injection, blood was drawn from Retro Orbital Plexus (RPO) of anaesthetized animal which were fasted overnight to check the fasting blood glucose. Rats with fasting blood glucose more than 250mg/dl were selected for the experimental group with 6 animals in each group.

(c) M*orus indica* powder at a level of 500mg/kg body weight was mixed with the diet and provided to the animals of MIP group. Animals of INS group were injected with insulin daily (5 units/kg body weight), whereas, Glibenclimide was dissolved in distilled water and fed orally (400µg/kg body weight) daily to the animals of GNB group (Sheela and Augusti, 1992). The animals were maintained with above treatment for a period of 45 days. The weights of the animals were monitored weekly. During the study period, daily food and water consumption was determined and expressed as intake/week ± SD.

### 2.3 Blood collection

At the end of the study period, the animals were fasted for 12h, anaesthetized (diethyl ether) and dissected, cardiac blood was collected immediately into test tube and allowed to clot for 30min at 2°C. The tubes were then centrifuged at 2500rpm for 20min in cold condition (4°C). The serum was aspirated into ependorff tubes and used for biochemical estimations. The liver was excised, washed with saline and weighed, phosphate buffered saline (pH 7.4) was added to liver 1:5 (w/v), and homogenized using Teflon pestle. The homogenate was centrifuged at 2500rpm (5min); the supernatant was used for the estimation of biochemical parameters.

### 2.4 Biochemical parameters

#### 2.4.1 Blood glucose

Blood from tail vein of the overnight fasted rats was drawn weekly and blood glucose was estimated immediately by Glucose-Oxidase Peroxidase kit (Span- India) in protein free supernatant. The threshold of urine sugar of the overnight fasted animals was determined weekly using Uristix.

#### 2.4.2 Estimation of G-6-P DH and aldolase activity

G-6-P DH and aldolase in the liver homogenate was estimated using standard diagnostic kits (Randox).

#### 2.4.3 Estimation of lipid peroxides

Lipid peroxides in the serum and liver homogenate were measured according to the method of Ojhawa, Ohishi and Yagi (1979). The lipid peroxidation products react with thiobarbituric acid forming a pink coloured adduct on boiling which was measured.

#### 2.4.4 Estimation of reduced glutathione

Reduced glutathione (GSH) in the serum and liver homogenate was estimated based on the reaction of 5,5'dithiobis-2-nitrobenzoic acid (DTNB) with compounds containing sulphydryl groups (Beutler, Duron and Kelly, 1963).

#### 2.4.5 Estimation of AsAT, AlAT, triglycerides and total cholesterol

AsAT, AlAT, Triglycerides and total cholesterol in the serum were estimated at the end of the study period using standard kits (Agappe).

### 2.5 Statistical analysis

Data were recorded as means ± standard deviation of duplicate measurements and subjected to one-way-ANOVA using SPSS software.

## 3. Results

The effect of *Morus indica* L. on fasting blood glucose, carbohydrate metabolizing enzymes (glucose-6-phosphate dehydrogenase and aldolase), total cholesterol and triglycerides were studied in control and streptozotocin induced diabetic rats.

The changes in the body weights, food and water intake in normal and diabetic rats are presented in Table 1. There was a significant ($p<0.05$) decrease in body weights of the diabetic control group at the end of the study period compared to other groups. The body weights of the animals treated with MIP, INS and GNB decreased at the end of first week, followed by a gradual increase ranging from 21-44% thereafter. In untreated diabetic rats, there was a significant decrease ($p<0.05$) in the body weight (20%) compared to normal rats. Oral administration of mulberry significantly increased the body weight, although food and water intake increased during the study period. It was significantly lower compared to diabetic control group.

The food consumption pattern of the animals is given in Table 1. The average weekly food intake was significantly low ($p<0.05$) in the experimental groups (MIP- 42.9g, INS - 47.8 g and GNB - 51.5g) compared to the healthy control group (67.8g), whereas the food intake of untreated diabetic group (88.8g) was higher compared to control group during the first week after induction of diabetes. Food intake of the experimental group increased from second week of the study period. The average weekly food intake of the treated groups was significantly low compared to diabetic control group. The average weekly water intake of the uncontrolled diabetic group was significantly high compared to other groups (Table 1).

A significant reduction in blood glucose was seen following treatment with *M. indica* powder from an initial level of 257± 69.4 to 148 ± 34.48 mg/dl at the end 45 days ($p<0.05$) (Table 2). A gradual decrease in the blood glucose of the MIP group was observed during the study period. After 6 weeks of treatment, the percent reductions were 72, 64 and 42 in the three groups treated with Insulin, Glibenclimide and MIP.

The activities of G-6-PDH and Aldolase in the liver of control and experimental rats are shown in Table 2. It was observed that the activity of aldolase significantly increased in diabetic rats, when compared with control rats ($p<0.05$). Oral administration of *M. indica* powder for 45 days significantly reversed the values which was almost comparable to control group. The activity of aldolase in the liver of MIP was 0.19u/g Protein.

Serum cholesterol (TC) and triglyceride (TG) levels in all five groups of animals are shown in Figure 1. The serum TC and TG levels were significantly higher in diabetic rats compared to those in normal rats. Treatment with MIP caused a significant reduction ($p<0.05$) in both TC and TGL compared to INS and GNB group.

It was observed that the lipid peroxides in the liver homogenate of MIP (0.22 ± 0.08Nm/mg P) was significantly low compared to DC (0.43 ± 0.03 Nm/mg P), and was almost similar to that of GNB (0.21 ± 0.04 nm/mg P). Serum MDA levels in the MIP group was 0.10 ± 0.03 nm/mg P which was significantly low compared to DC (0.29 ± 0.03 nm/mg P), INS (0.15 ± 0.02 nm/mg P) and GNB (0.21 ± 0.06 nm/mg P). Supplementation of *Morus indica* significantly increased the GSH content (2.87 ± 1.72µm/mg P) which was significantly high compared to DC (0.55 ± 0.10 µm/mg P) and GNB (1.07 ± 0.39µm/mg P) whereas, the GSH content of INS group (3.91 ± 0.10 µm/mg P) was significantly high compared to other experimental group. Serum GSH in MIP group was significantly high (0.18 ± 0.05 µm/mg P) compared to DC (0.05 ± 0.01 µm/mg P), whereas it was comparable to INS (0.17 ± 0.03 µm/mg P) and GNB (0.17 ± 0.03 µm/mg P). Induction of diabetes elevated the activity of AsAT and AlAT in the animals, urea, creatinine and lipid peroxides, treatment with *Morus* significantly ($p<0.05$) restored these parameters to near normal levels in diabetic rats.

## 4. Discussion

In the present study, increased food and water consumption was observed in the experimental groups in comparison to normal rats, indicating polydypsia and loss of body weight due to excessive breakdown of tissue proteins (Kameswararao *et al*., 2003). In an earlier study also, it is reported that supplementation of *M. indica* powder decreased the food intake and there was a gradual increase in the body weights of the animals compared to control diabetic group (Andallu and Varadacharyulu, 2003). Increase in the body weights in the experimental groups may probably be due to the improvement in insulin secretion and *glycemic* control. Similar observations have been reported in the diabetic animals treated with *Ficus bengalensis* and *Trigonella foenum greacum* (Kameswararao *et al*., 2003). Treatment with mulberry decreased food consumption and improved body weight to some extent indicating control over polyphagia and muscle wasting resulted due to hyperglycemic condition. Data on blood glucose of the present study indicates that MIP is effective in lowering the blood glucose indicating the antihyperglycemic effect of *Morus indica*.

Liver acts as a "glucostat" and plays a vital role in the maintenance of blood glucose level and, hence, it was of interest to examine the possible role of *Costus igneus* on enzymes of carbohydrate metabolism in liver. Aldolase, one of the key enzymes in the glycolytic pathway, increases in diabetes and this may be due to cell impairment and necrosis (Ragavan and Krishnakumari, 2006). The higher activity of Glucose-6-phosphate dehydrogenase in the liver of MIP group compared to untreated diabetic group suggests the utilization of glucose by citric acid cycle and the pentose pathway (Khan *et al*., 1995). The reduction in the blood glucose of the experimental groups may be due to higher rate of glycolysis as evidenced by the activity of aldolase and Glucose-6-phosphate dehydrogenase, two of the key enzymes of Glycolysis (Ragavan and Krishnakumari, 2006).

The activity of AsAT and AlAT are cystolic marker enzymes reflecting hepatocellular necrosis as they are released into the blood after cell membrane damage. Therefore, we use the activities of AsAT and AlAT in the circulation as indicators of hepatic damage (Kim *et al*., 2006). In the present study, treatment with *Morus* effectively reduced serum AsAT and AlAT activities suggesting that the plant could prevent hepatic injury associated with diabetes.

Many active compounds have been isolated from the plant and herb species of India. These active principles are dietary fibers, alkaloids, flavonoids, saponins, amino acids, steroids, peptides and others. These have produced potent hypoglycemic, anti-hyperglycemic, and glucose suppressive activities (Gupta *et al*., 2008). The above effect of *Morus* may be due to insulin release from pancreatic β-cells, inhibited glucose absorption in gut, stimulated glycogenesis in the liver or increased utilization by the body (Grover *et al*., 2002). These compounds are also reported to exhibit their antioxidant, hypolipidemic, restored enzymatic functions, repair and regeneration of pancreatic islets and the alleviation of liver and renal damage (Mukherjee *et al*., 2006). It is reported that the compounds of mulberry leaves, particularly fagomine, is capable of inducing insulin secretion in isolated rat

**Table 1:** Changes in body weights, food and water consumption patterns of rats treated with *Morus indica* **L.**

| Rat group | Body weight(g) | | | | Food intake (g) | | | | Water intake (ml) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial | 2nd wk | 4thwk | 6th wk | 1st wk | 2nd wk | 4th wk | 6th wk | 1st wk | 2nd wk | 4th wk | 6th wk |
| NC | 144 ± 17.2 | 184 ± 9.9 | 209 ± 7.7 | 231 ± 9.3 | 67.8 ± 7.7 | 68.7 ± 3.7 | 112.6 ± 4.3 | 138 ± 9.9 | 57.2 ± 6.1 | 72.5 ± 2.8 | 98.8 ± 5.4 | 118 ± 8.0 |
| DC | 192[a] ± 7.5 | 181[a] ± 6.5 | 161[a] ± 7.3 | 152[a] ± 5.5 | 88.8[a] ± 6.5 | 101.0[a] ± 2.5 | 136.4[a] ± 8.2 | 177[a] ± 6.5 | 93.4[a] ± 7.2 | 104.2[a] ± 8.3 | 145.6[a] ± 7.5 | 168[a] ± 5.8 |
| MIP | 156[b] ± 13.4 | 149[b] ± 10.2 | 173[b] ± 11.4 | 190[b] ± 30.4 | 42.9[b] ± 2.5 | 81.8[b] ± 3.7 | 128.9[b] ± 10.5 | 158[b] ± 13.9 | 43.4[b] ± 2.5 | 86.8[b] ± 2.7 | 136.5[b] ± 3.4 | 161[b] ± 4.8 |
| INS | 155[b] ± 17.9 | 179[c] ± 21.7 | 198[c] ± 11.7 | 224[c] ± 17.0 | 47.8[c] ± 3.8 | 73.4[c] ± 4.5 | 118.4[c] ± 6.2 | 151[c] ± 11.2 | 40.4[c] ± 4.1 | 75.3[c] ± 3.6 | 120.6[c] ± 5.8 | 148[c] ± 10.4 |
| GNB | 157[b] ± 16.0 | 168[c] ± 15.8 | 180[d] ± 17.3 | 204[d] ± 17.2 | 51.5[d] ± 3.1 | 80.2[d] ± 3.0 | 126.2[d] ± 3.5 | 162[d] ± 5.8 | 43.5[b] ± 3.4 | 83.0[d] ± 8.6 | 131.4[d] ± 4.5 | 158[d] ± 4.7 |

Mean values carrying superscripts a, b, c and d in columns differ significantly ($p<0.05$) between groups.
NC- Normal control, DC- Diabetic control, MIP – *Morus indica* leaves powder, INS-Insulin, GNB-Glibenclamide. (n=6 in each group)

**Table 2:** Blood glucose, glucose-6-phosphate dehydrogenase and aldolase levels of the animals

| Rat group | Blood glucose (mg/dl) | | | | Enzymes (liver) | |
|---|---|---|---|---|---|---|
| | Initial | 2nd wk | 4th wk | 6th wk | G-6-PDH (mIU/mg P) | Aldolase (mIU/mg P) |
| NC | 81 ± 11.3[a] (1± 0.0) | 79 ± 5.24[b] (1 ± 0.0) | 80 ± 7.03[c] (1 ± 0.0) | 82 ± 3.61[d] (1 ± 0.0) | 1.16 ± 0.28 | 0.16 ± 0.03 |
| DC | 286 ± 25.0[al] (4 ± 0.001) | 460 ± 63.7[bl] (4 ± 0.001) | 473 ± 26.8[cl] (4 ± 0.001) | 481 ± 25.11[dl] (4 ± 0.001) | 0.54 ± 0.04[a] | 0.24 ± 0.03[a] |
| MIP | 257.00 ± 69.41[am] (4 ± 0.001) | 158 ± 10.30[bm] (1 ± 0.00) | 146 ± 12.16[cm] (1 ± 0.00) | 148.8 ± 4.48[dm] (1 ± 0.00) | 1.08 ± 0.48[b] | 0.19 ± 0.07[b] |
| INS | 345 ± 57.44[an] (4 ± 0.001) | 109 ± 6.29[bn] (1 ± 0.00) | 101 ± 2.08[cn] (1 ± 0.0) | 101 ± 1.91[cn] (1 ± 0.0) | 0.98 ± 0.10[c] | 0.19 ± 0.02[b] |
| GNB | 364 ± 34.52[ao] (4 ± 0.001) | 149 ± 9.95[bo] (1 ± 0.00 ) | 142 ± 5.75[cm] (1 ± 0.0) | 123 ± 19.54[do] (1 ± 0.0) | 1.04 ± 0.42[b] | 0.18 ± 0.05[b] |

NC- Normal control, DC- Diabetic control, MIP – *Morus indica* leaves powder, INS-Insulin, GNB-Glibenclamide. n= 6 in each group.
Mean values carrying superscripts a, b, c and d in rows within the group and l, m, n, o in columns between groups differ significantly ($p<0.05$)

**Table 3:** Biochemical parameters of the normal and streptozotocin induced diabetic animals

| Animal group | Liver homogenate | | Serum | | | | | |
|---|---|---|---|---|---|---|---|---|
| | MDA (nm/mg P) | GSH (µm/mg P) | MDA (nm/mg ) | GSH (µm/mg P) | AsAT (u/ml) | AlAT (u/ml) | Urea (mg/dl) | Creatinine (mg/dl) |
| NC | 0.05 ± 0.01 | 1.28 ± 0.26 | 0.08 ± 0.01 | 0.27 ± 0.26 | 53.3 ± 2.3 | 42.3 ± 1.51 | 23.03 ± 1.47 | 0.80 ± 0.07 |
| DC | 0.43 ± 0.03[a] | 0.55 ± 0.10[a] | 0.29 ± 0.03[a] | 0.05 ± 0.01[a] | 256.6 ±70.9[a] | 65.4 ± 19.1[a] | 68.94 ± 7.03[a] | 1.26 ± 0.17[a] |
| MIP | 0.22 ± 0.08b | 2.87 ± 1.72[b] | 0.10 ± 0.03[b] | 0.18 ± 0.05[b] | 109.2 ± 26.1[b] | 50.0 ± 16.0 | 42.8 ± 11.98[b] | 0.78 ± 0.31 |
| INS | 0.16 ± 0.01[c] | 3.91 ± 0.10[c] | 0.15 ± 0.02[c] | 0.17 ± 0.03[b] | 96.3 ± 21.4[c] | 47.6 ± 14.3[c] | 42.58 ± 5.3[b] | 0.84 ± 0.48[c] |
| GNB | 0.21 ± 0.04[b] | 1.07 ± 0.39[d] | 0.21 ± 0.06[b] | 0.17 ± 0.03[b] | 102.5 ± 28.3[d] | 52.8 ± 9.2[b] | 36.28 ± 7.27[c] | 1.04 ± 0.35[d] |

NC- Normal control, DC- Diabetic control, MIP-*Morus indica* leaves powder, INS-Insulin, GNB-Glibenclamide. n= 6 in each group.
Mean values carrying superscripts a, b, c and d in columns differ significantly ($p<0.05$) between groups.

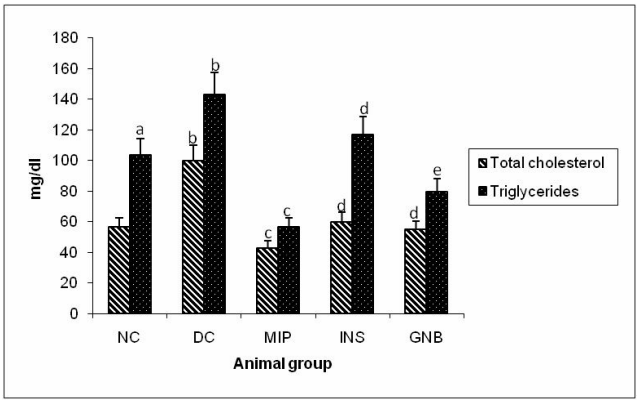


**Figure 1:** Lipid profile of the normal and streptozotocin induced diabetic animals.

NC- Normal control, DC-Diabetic control, MIP-*Morus indica* leaves powder, INS-Insulin, GNB-Glibenclamide.

islet cells (Taniguchi *et al*., 1998). It is known that insulin resistance in type 2 diabetes is not confined only to glucose metabolism but also covers fatty acid metabolism. The concurrent effect of *Morus indica* therapy on fatty acid metabolism was significant in diabetic animals, this was evidenced by the reduction of serum cholesterol, triglycerides and lipid peroxides in animals treated with *Morus indica*.

Compared to an earlier study reporting blood glucose lowering effect at a level of 25% supplementation (Shukla *et al*., 2000) in the present study, much lower levels of mulberry (500 mg/kg b.wt) decreased blood glucose levels similar to the effect shown by standard drugs.

## Conclusion

Research on medicinal plants *per se* could provide useful leads towards the development of newer alternatives for the treatment. From this experimental data, it is evident that mulberry leaves efficiently regulated blood glucose in diabetic rats, restored the elevated activity of the carbohydrate metabolic enzymes and also ameliorated lipid abnormalities associated with diabetes in STZ-diabetic rats.

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## Conflict of interest

We declare that we have no conflict of interest.

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