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Hypoglycemic and hypolipidemic activity of *Ficus mollis* leaves

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Abstract: The present research was designed to evaluate the hypoglycemic and hypolipidemic activity of ethyl acetate extract of *Ficus mollis* Vahl, Moraceae, against dexamethasone induced insulin resistance. Wistar albino rats were treated with dexamethasone (10 mg/kg) for ten days to induce insulin sensitivity. Hypoglycemic and hypolipidemic activity of ethyl acetate extract of *F. mollis* were evaluated by using two different doses (200 and 400 mg/kg body weight *p.o.*). The day 11 all rats were sacrificed and serum was collected for biochemical estimation, liver and pancreas were excised for histopathology. Administration of dexamethasone shows hyperglycemia and hyperlipidemia due to insulin resistance. Ethyl acetate extract of *F. mollis* reverted the hyperglycemia and hyperlipidemia caused by dexamethasone in a dose dependent manner. The changes were further confirmed by histopathological report. The extract effect was compared with reference standard glibenclamide, which shows a similar effect. From these findings it has been concluded that the ethyl acetate extract of *Ficus mollis* offered significant protection against dexamethasone induced hyperglycemia and hyperlipidemia.

Article

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Introduction

Diabetes is a global disease with a huge adverse effect on health and mortality, particularly diabetes is a major risk factor for cardiovascular disorders. Diabetes occurs at any time of life from infancy to old age. Type-2 diabetes is primarily a lifestyle disorder. This accounts for around 90% of diabetes cases and increasing at an astonishing rate in developing countries like India. In 1995, it has been estimated that around 135 million people had this condition, and this may increase to as many as 300 million by the year 2025 (King et al., 1998).

Liver is an important organ, which plays a pivotal role in glucose and lipid homeostasis and is severely affected during diabetes (Seifter & England, 1982). During diabetes a profound alteration in the concentration and composition of lipid occurs (Sochar et al., 1995). Decreased glycolysis, impeded glycogenesis and increased gluconeogenesis are some of the changes of glucose metabolism occur in the diabetic liver. *Diabetes mellitus* is known to cause hyperlipidemia through various metabolic disarrangements. Among several metabolic disarrangements, insulin deficiency has been known to stimulate lipolysis in the adipose tissue and give rise to hyperlipidemia and fatty liver. Thus, in diabetes hypercholesterolemia and hypertriglyceridemia often occur (Davis & Granner, 1996).

Dexamethasone, a very potent and highly selective glucocorticoid used in the treatment of inflammatory disorders. Patients are using glucocorticoids as steroidal supplement, which profoundly affect carbohydrate and protein metabolism. Teleologically, these effects of glucocorticoids on intermediary metabolism can be viewed as protecting the glucose-dependent tissues (*e.g.*, the brain and heart) from starvation. They stimulate the liver to form glucose from amino acids and glycerol and to store glucose as glycogen in the liver. In the periphery tissue, glucocorticoids diminish glucose utilization, increase protein breakdown by increasing the synthesis of glutamine and lipolysis, thereby providing amino acids and glycerol for gluconeogenesis. The net result is to increase blood glucose levels. Glucocorticoids can worsen glycemic control in patients with overt diabetes and can precipitate the onset of hyperglycemia in patients who are otherwise predisposed (Bernard et al., 2006).

Ficus mollis Vahl synonym: *Ficus tomentosa* (Roxb) belongs to family Moraceae is the large tree distributed in rocky, hilly and dry lands (Madhava Chetty et al., 2008). The genus is remarkable for the large variation in the habits of its species. *Ficus mollis* used for a variety of diseases in traditional medicine. The leaves of *F. mollis* along with leaves of *Madhuca indica* were used to relieve the pain in the ear (Venkataramana & Venkataraju, 2004). Alcoholic

extracts of leaves and bark of *Ficus mollis* shown good antibacterial activity (Sreenivasulu et al., 2009). The present research was made to investigate the potential hypoglycemic and hypolipidemic effect of *Ficus mollis* in dexamethasone-induced insulin resistance in rats.

Materials and Methods

Collection and identification of plant

The leaves of *Ficus mollis* Vahl, Moraceae, were collected from Talakona forest, Chittor Dist, Andhra Pradesh in the month of June, 2007 and identified by Dr. K. Madhava Chetty, Department of Botany, Sri Venkateswara University, Tirupathi. The voucher specimen (ANCP-MP-89) has been deposited in the parent department.

Animals

Wistar albino rats (175-200 g) of both male and female were obtained from the Institute Animal House and maintained at 25±2 °C temperature and relative humidity 45-55% under 12:12 h light:dark cycle. Rats were fed with standard rat chow and water *ad-libitum*. The protocol was approved by the Institute's Animal Ethical Committee (1220/a/08/CPCSEA).

Preparation of the plant extract

About 150 g of dried leaves of *F. mollis* were taken in a 5000 mL of the round bottom flask and extracted for 72 h by a continuous hot percolation process using different solvents according to the increasing polarity; likewise pet ether, benzene, chloroform, acetone, ethyl acetate, methanol, ethanol, water. The extracts were filtered through the Whatmann filter paper to remove impurities. The extracts were then concentrated by vacuum distillation, cooled and placed in desiccators to remove the excessive moisture.

Phytochemical analysis

The concentrated extracts were subjected to chemical test as per the methods mentioned in the reference book for the identification of the various constituents (Harborne, 1998).

Acute toxicity studies

Ethyl acetate extract of *F. mollis* was administered orally through gastric intubation in 5% Tween-80 (T80) used as a surfactant at doses of 500, 1000, 1500, 2000 and 3000 mg/kg bw and control group received 0.5 mL of 5% T80. The animals were observed continuously for 72 h for any signs of behavioral changes, toxicity and mortality.

Dexamethasone induced hyperglycemia and hyperlipidemia

Animals were divided into five groups, each consisting of six rats. Rats in the first group received vehicle and served as a control group, while the second group of rats received vehicle plus dexamethasone (10 mg/kg *s.c*.) and served as a positive control group. Rats in experimental groups 3 were treated with glibenclamide (500 µg/mg *p.o*.) plus dexamethasone, whereas rats in the 4th and 5th group were treated with ethyl acetate extract of *F. mollis* (200 and 400 mg/kg *p.o*., dose selected from acute toxicity studies) plus dexamethasone. All the animals received their respective assigned treatment daily for a period of ten days. Rats of group 2-5 were daily fasted over night before dexamethasone treatment. On day 11, the animals were anesthetized with ether, and blood was collected from retro orbital plexus. Serum was then separated for the estimation of glucose, cholesterol, triacylglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) along with transaminases (SGOT, SGPT) by using respective kits purchased from Span Diagnostics, Pune.

Statistics

All the results were expressed as mean±SEM, and the data were analyzed using one way ANOVA followed by Student newman keuls post test using GraphPad Prism software $p<0.05$ was considered significant.

Results

Phytochemical tests

Various phytochemical tests were performed for the pet ether, chloroform and ethyl acetate extract of *F. mollis*. The phytochemical evaluations showed the presence of triterpenoids and flavonoids in ethyl acetate extract.

Acute toxicity study

There was no mortality or any signs of behavioral changes or toxicity observed after oral administration of ethyl acetate extract of *F. mollis* up to the dose level of 3000 mg/kg bw in rats.

Dexamethasone induced hyperglycemia and hyperlipidemia

There is significant ($p<0.01$) increase in the level of Glucose, cholesterol, LDL, triacylglycerides, SGOT, SGPT and significant ($p<0.05$) decrease in the level of

Table 1. Effect of *Ficus mollis* extract on dexamethasone induced hyperglycemia and hyperlipidemia.

Group	Glucose mg/dL	Cholesterol mmol/L	HDL mmol/L	LDL mmol/L	Triacylglyceride mmol/L	SGOT IU/L	SGPT IU/L
G1	97.5±0.5	67.5±0.5	23±2	35±0	61±1	203±1	82.5± 0.5
G2	172±2**	129±3**	15.5±0.5*	44.5±1.5*	99.5±0.5**	475±5.5**	177.5±1.5**
G3	137±5^{a}	77.5±0.5^{a}	18.5±0.5^{ns}	39.5±0.5^{ns}	81.5±1.5^{ns}	226.5±0.5^{a}	90.5±0.5^{b}
G4	147.5± 5.5^{b}	81±1^{a}	22.5±0.5^{b}	43.5±2.5^{ns}	82±11^{ns}	269± 9^{a}	94.5±.5^{b}
G5	123.5± 7.5^{a}	88±8^{a}	16.5±0.5^{ns}	37.5±2.5^{ns}	63.5±2.5^{b}	305±6.5^{a}	77.5±0.5^{b}

All values are expressed as mean±SEM. One way ANOVA followed by Dunnet's post test. *p<0.05; **p<0.01 Vs C. ^{a}p<0.05; ^{b}p<0.01 Vs NC. ^{ns}: non specific; G1: control group treated with saline; G2: negative control group which is treated with dexamethasone; G3: positive control group which is treated with dexamethasone and Glibenclamide; G4: ethyl acetate extract of *Ficus mollis* (200 mg/kg) treated animal group; G5: ethyl acetate extract of *Ficus mollis* (400 mg/kg) treated animal group.

HDL in dexamethasone induced rats when compared with vehicle treated rats. Ethyl acetate extract of *F. mollis* significantly (p<0.01 and p<0.05) decreased the level of glucose, cholesterol, LDL, triacylglycerides, SGOT, SGPT and significantly (p<0.01 and p<0.05) increased the level of HDL in two different doses. There are significant changes in the level of glucose, cholesterol, triacylglycerides, SGOT, and SGPT in glibenclamide treated rats (Table 1).

The liver of the rats treated with saline showing the normal architecture of the hepatocytes (Figure 1a). The liver of the rats treated with dexamethasone showing degeneration of hepatic cords and inflammation (Figure 1b). The liver of the rats treated with glibenclamide showing the normal architecture of the rats hepatocytes without inflammation (Figure 1c). The liver of the rats treated with *F. mollis* showing the regeneration of hepatic cords with minimal inflammation (Figure 1d,e). Rat pancreas treated with saline showing normal parenchymatous cell without any degeneration and inflammation (Figure 2a). Rat pancreas treated with dexamethasone showing degeneration pancreatic cells and with inflammation vacuoles (Figure 2b). Rat pancreas treated with glibenclamide showing mild changes in the cells of the pancreas without inflammation (Figure 2c). Rat pancreas treated with *F. mollis* does not show a marked inflammation collection in the pancreatic cells (Figure 2d,e).

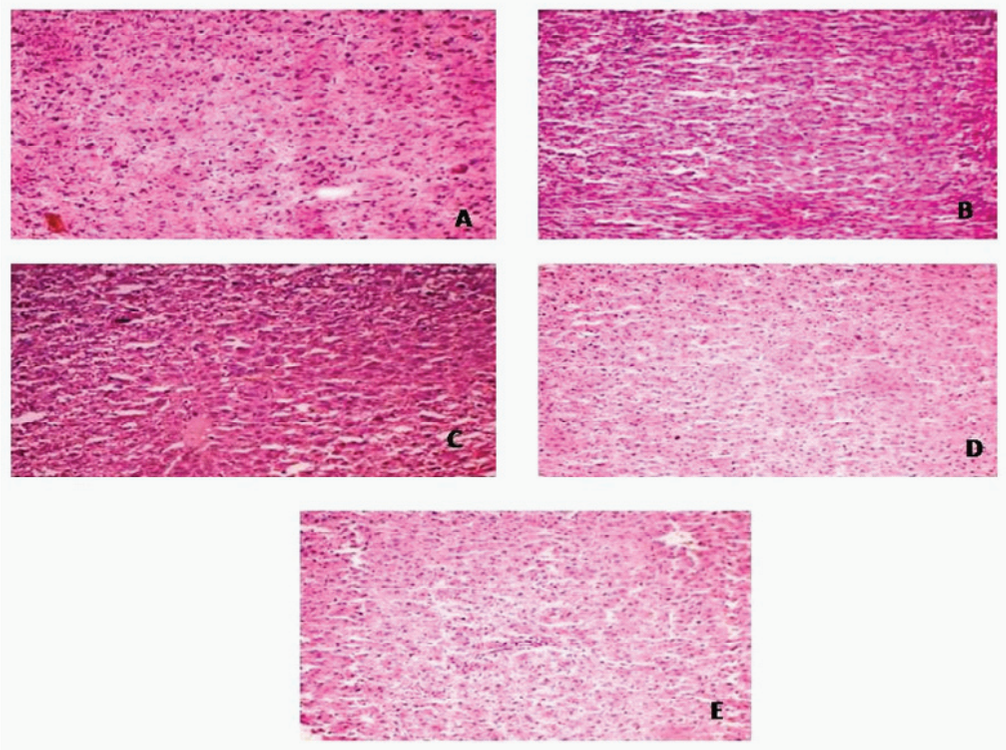

Figure 1. Histopathology of liver. A. The liver of the rats treated with saline; B. The liver of the rats treated with dexamethasone; C. The liver of the rats treated with glibenclamide; D. The liver of the rats treated with *Ficus mollis* (200 mg/kg); E. The liver of the rats treated with *F. mollis* (400 mg/kg).

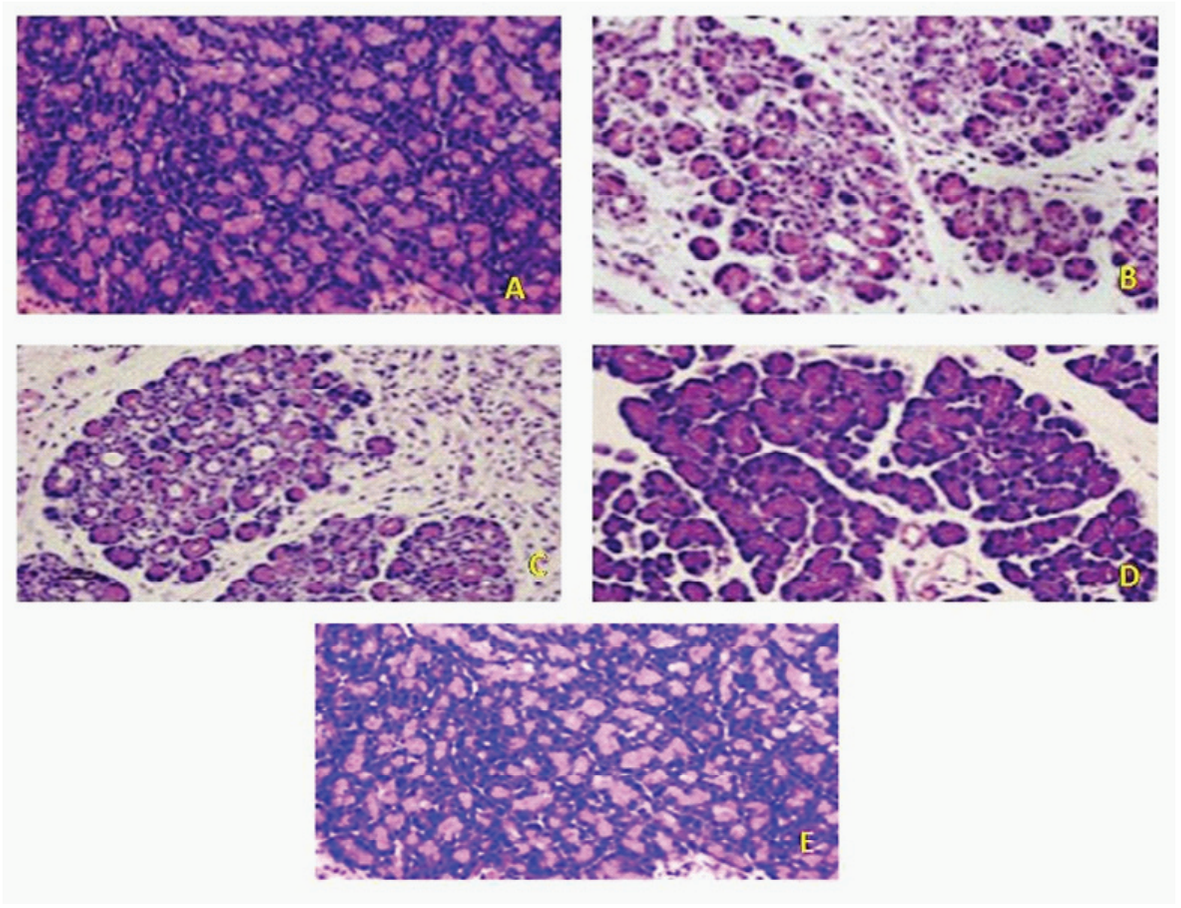

Figure 2. Histopathology of pancreas. A. The liver of the rats treated with saline; B. The liver of the rats treated with dexamethasone; C. The liver of the rats treated with glibenclamide; D. The liver of the rats treated with *Ficus mollis* (200 mg/kg); E. The liver of the rats treated with *F. mollis* (400 mg/kg).

Discussion

Insulin resistance in type-2 diabetes is not only associated with hyperglycemia but also with hyperlipidemia and atherosclerosis (DeFronzo et al., 1992; Reaven,1988). Insulin resistance in humans has been shown to be present in conditions like Non Insulin Dependant Diabetes Mellitus (NIDDM), obesity and dyslipidemia. Thus interventions to decrease insulin resistance may postpone the development of NIDDM and its complications. By treatment with natural herbs we may find lesser side effects compared to the presently used synthetic oral antidiabetic agents.

In the present study it was found that the elevation of serum glucose and abnormal changes in the lipid profile in dexamethasone treated rats showed the hyperglycemia and hyperlipidemia caused by this drug. Dexamethasone increases triacylglyceride levels, caused an imbalance in lipid metabolism leading to hyperlipidemia (Wiesenberg et al., 1998) and an increase in glucose levels leading to hyperglycemia (Mahendran & Devi, 2001). Pharmacological doses of glucocorticoids induce the gene expression in rat adipocyte tissue within 24 h. This is followed by complex metabolic changes resulting in a decrease in food consumption; reduction in body weight, profound obesity often accompanied by diabetes and the development of insulin resistance with enhanced blood glucose and triacylglyceride levels. Ethyl acetate extract of *F. mollis* prevented the rise in triacylglyceride, glucose, cholesterol and LDL caused by dexamethasone. Further, this also prevented the progressive decrease in HDL and body weight caused by dexamethasone. The phytochemical screening shows the presence of flavonoids and triterpenoids in all the extract. The concentration of flavonoids is more in the ethyl acetate extract which might be a responsible active principle for these effects.

Conclusion

The ethyl acetate extract of *Ficus mollis* gave the positive result to the flavonoids and triterpenoids in phytochemical studies. The flavonoids present in the *Ficus mollis* leaves may be responsible for hypoglycemic

and hypolipidemic activity. Two different doses of ethyl acetate extract were selected for the acute toxicity studies is 200 and 400mg/kg. Among the two, 200 mg/kg dose has shown better results than the 400 mg/kg. At 400mg/kg dose the animals shown little toxicity and minor damage in the pancreatic cells.

Author contributions

MS contributed in collecting plant samples and identification, a confection of herbarium, running the laboratory work, analysis of the data and drafted the paper. MSTS contributed to biological studies. MS and MSTS designed the study, supervised the laboratory work and contributed to critical reading of the manuscript. All the authors have read the final manuscript and approved the submission.

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