ORIGINAL ARTICLE

Anti-diabetic effect of hydroalcoholic extract of *Ficus palmata* Forsk leaves in streptozotocin-induced diabetic rats

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Context: *Ficus palmata* Forsk, commonly known as wild fig (also known as bedu) is the member of genus Ficus of the family Moraceae. It has been used traditionally in various ailments including diabetes. **Aim:** The aim of the present study was to investigate anti-diabetic effect of *Ficus palmata* forsk leaves extract in normal, glucose-loaded hyperglycaemic and streptozotocin (STZ)-induced diabetic rats. **Materials and Methods:** Diabetes was induced by intraperitoneal administration of STZ (45 mg kg^{-1}). The effect of oral administration of *F. palmata* at 50, 100 and 200 mg kg^{-1} was studied in normal, glucose-loaded and STZ-diabetic rats. **Results:** All three doses of *F. palmata* caused significant ($P < 0.001$) reduction in blood glucose levels. The effect was more pronounced at doses of 100 and 200 mg kg^{-1}. *F. palmata* also showed significant ($P < 0.001$) increase in serum insulin, body weight and glycogen content in liver and skeletal muscle of STZ-induced diabetic rats while there was significant reduction in the levels of serum triglyceride and total cholesterol. *F. palmata* also showed significant anti-lipid peroxidative effect in the pancreas of STZ-induced diabetic rats. **Statistical Analysis:** All values were expressed as mean ± SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests using GraphPad Prism 5. The results were considered statistically significant if $P < 0.05$. **Conclusion:** The results obtained in this study indicate that the hydroalcoholic extract of *F. palmata* leaves possesses significant anti-diabetic activity associated with anti-hyperlipidaemic and anti-lipid peroxidative effects.

Key words: Anti-diabetic, anti-hyperlipidemic, anti-lipid peroxidative, diabetes mellitus, *Ficus palmata*

INTRODUCTION

Diabetes mellitus (DM) is a global health problem and it was increasing constantly. The number of diabetic people is expected to rise to 366 million in 2030 and most common of them were type 2 diabetes. It consists of a group of syndromes characterised by hyperglycaemia; altered metabolism of lipids, carbohydrates and proteins and an increased risk of complications from vascular disease.[1] Conventional treatment for the management of diabetes mellitus includes oral hypoglycaemic agents and insulin but there is a burden of unwanted side effects such as hypoglycaemia, diarrhoea, nausea, dyspepsia, myocardial infarction, peripheral oedema and dizziness with these synthetic drugs. Therefore, search for natural anti-diabetic plant products for controlling diabetes is going on.[2] The plants secondary metabolites are potentially effective for the complicated disorders like diabetes.[3] Various species of Ficus such as *F. arnottiana* Miq. Bark,[4] *F. bengalinsis* Linn,[5] *F. glomeruata*,[6] *F. religosa*[7] and *F. hispida* Linn. Bark[8] has been studied for their anti-diabetic and ameliorative activity. Ficus species of the Moraceae family are used in folk medicine for the treatment of various diseases such as biliousness,[9] ulcers,[10] vomiting,[11] inflammations,[12] leucoderma,[13] diuretic,[10] leprosy,[14] hepatoprotective[15] and antifungal. Different phytoconstituents which has been reported in the *F. palmata* are flavanoids, glycosides, alkaloids, phenolic acids, steroids, saponins, coumarins, tannins, etc., Various compounds isolated from leaves, bark and heartwood of *F. palmata* are gallic acid and ellagic acid, β-sitosterol, sigmasterol and a new tetracyclic tritepene - glaunol acetate. Besides ceryl behenate, lupeol, α- amyrin, β-amryin acetate are reported from the stem bark of *F. palmata*.[16] Based on its uses in traditional Indian medicine, the hydroalcoholic extract of the leaves of *F. palmata* was investigated for anti-diabetic activity in this study.

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MATERIALS AND METHODS

Chemicals

Streptozotocin and glibenclamide were purchased from Sigma Chemical Company (St. Louis, USA).

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All other chemicals and reagents used were of analytical grade.

Plant Material

The leaves of *F. palmata* were collected from Uttarkashi district in Uttarakhand (India) in winter 2012. The plant was authenticated by Dr. S. N. Sharma of the Department of Taxonomy, Indian Institute of Integrative Medicine (IIIM), Canal road, Jammu.

Preparation of Plant Extract

The leaves of *F. palmata* were air-dried and coarsely powdered. The plant material was then extracted with methanol and water (1:1). The extract obtained was then filtered through Whatman filter paper. The filtrate was lyophilised giving a dark green solid with a yield of 2.8% (w/w). The extract was stored in refrigerator.

Preliminary Phytochemical Screening and Estimation of Total Phenolics and Total Flavonoid Content of Hydroalcoholic Extract

The extract of *F. palmata* was subjected to preliminary qualitative chemical screening.[17,18] Estimation of total phenolic content was done by the Folin-Ciocalteu's method and flavonoid content was determined by aluminium chloride colorimetric assay using gallic acid and quercetin as standards, respectively.[19,20]

Experimental Animals

Albino wistar rats of either sex weighing between 150 and 200 gm were procured form registered breeders (LAR, CPCSEA No-196, IVRI, Bareilly). The animals were housed under standard conditions of temperature (25 ± 2°C) and relative humidity (30-70%) with a 12:12 light-dark cycle. The animals were fed with standard pellet diet (VRK Nutrition, Pune) and water *ad libitum*. All the studies conducted were approved by the Institutional Animal Ethical Committee (1435/PO/a/11/CPCSEA).

Experimental Design

The anti-diabetic activity of *F. palmata* was assessed in normal, glucose-loaded hyperglycaemic and streptozotocin-induced diabetic rats. Rats were generally fasted overnight for 18 h with free access to water before the commencement of experiments.

Evaluation of Effect of Extract on Normal Healthy Rats

At the end of the 18 h fasting period, taken as zero time (0 h), blood was withdrawn from the tail vein under mild ether anaesthesia. Serum was separated by centrifugation (5000 rpm for 15 min.) and glucose was estimated using the GOD-POD method by means of commercial diagnostic kit (Siemens Healthcare Diagnostics Ltd., Baroda, India).[21] The animals were then randomly divided into four groups of six animals each. Group I served as control and received distilled water 10 ml kg^{-1} orally. Groups II, III and IV received *F. palmate* at doses of 50, 100 and 200 mg kg^{-1}. Blood glucose levels were determined at 1, 2, 3 and 4 h post-treatment [Figure 1].

Evaluation of Effect of Extract in Oral Glucose Tolerance Test

Healthy rats were divided into four groups of six animals each; Group I served as control and received only vehicle (distilled water; 10 ml kg^{-1} p.o.) and Groups II, III and IV received *F. palmata* at the dose level of 50,100 and 200 mg kg^{-1} p.o., respectively. All the animals were given glucose (2 g kg^{-1}) 60 min after dosing. Blood samples were collected from the tail vein under mild ether anaesthesia just prior to 0 min. (initial blood glucose level) and at 30, 60, 90 and 120 min after the glucose loading and blood glucose levels were estimated [Figure 2].[22]

Evaluation of Extract in Streptozotocin-induced Diabetic Rats

Experimental diabetes was induced by single intraperitoneal injection of 45 mg kg^{-1} of streptozotocin (STZ), freshly dissolved in cold citrate buffer pH 4.5. Control animals received only citrate buffer (10 ml kg^{-1}, p.o.). After 5 days of STZ injection, animals with fasting blood glucose level above 250 mg dl^{-1} were considered as diabetic and included in the study.[23] The animals were randomly assigned into six groups ($n = 6$). Group I served as control and received only vehicle and Group III, IV and V received *F. palmata* at the dose level of 50, 100 and 200 mg kg^{-1}, respectively whereas VI group received standard drug Glibenclamide (10 mg kg^{-1}).

Biochemical Analysis

Serum glucose analysis was done by GOD-POD method by means of commercial diagnostic kit (Siemens Healthcare Diagnostics Ltd., Baroda, India). Other serum estimations were done spectrophotometrically using standard

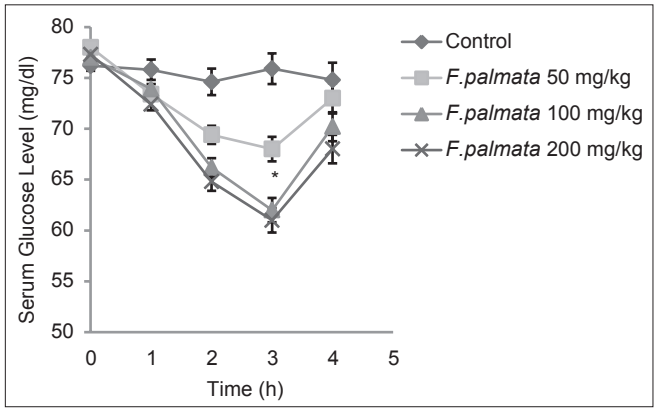

Figure 1: Effect of *F. palmata* on blood glucose levels in normoglycaemic rats. Each value is expressed as mean of five observations.*$P < 0.05$ when compared with values of 0 h of the same group

kits available which includes serum insulin (Mercodia AB, Sylveniusgatan 8A, Sweden), serum triglycerides by GPO-Trinder method (Siemens Medical Solutions Diagnostics Ltd., Baroda, India) and serum total cholesterol, CHOP-PAP method (Siemens Medical Solutions Diagnostics Ltd., Baroda, India). Glycogen was estimated in liver and skeletal muscle by the method of Halliwell and Gutteridge, 1990.[24] *In vivo* lipid peroxidation, expressed as TBARS (Thiobarbituric Acid Reactive Substances) was estimated in the pancreatic tissue homogenate according to the method of Ohkava *et al*., 1979[25] [Figure 3].

Acute Oral Toxicity Study

Acute oral toxicity of *F. palmata* was performed on Swiss Female albino mice according to Botham, 2004.[26] Two *F. palmata* groups of three rats each were used for the study. Group I served as control and received distilled water. Group II received single oral dose of *F. palmata* (2000 mg kg^{-1}). The animals were observed for gross behavioural, neurological, autonomic and toxic effects at short intervals of time for 24 h and then daily for 14 days.

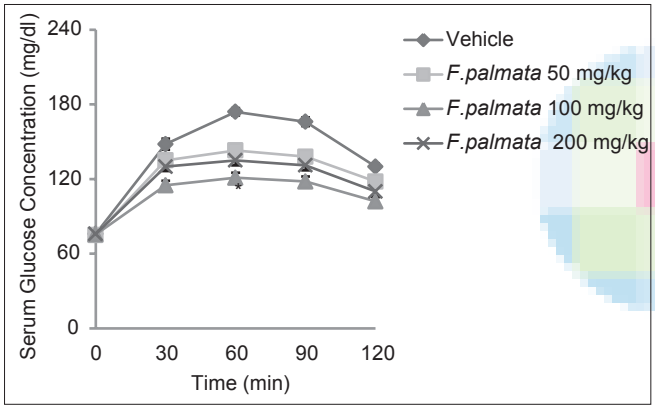

Figure 2: Effect of *F. palmata* on oral glucose tolerance in rats. Each value is expressed as mean of six observations. **P* < 0.05 when compared with corresponding values of the control group

Food consumption was monitored daily and body weights were recorded weekly. On 14th day, animals were sacrificed and all the organs were removed for gross pathological examination.

Statistical Analysis

All values were expressed as mean ± SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests using GraphPad Prism 5 (GraphPad Software, Inc., CA, USA). The results were considered statistically significant if $P < 0.05$.

RESULTS

Preliminary Phytochemical Analysis

The qualitative chemical tests of hydroalcoholic extract of *F. palmata* revealed the presence of tannins, flavonoids, polyphenols and carbohydrates. The total phenolic and flavonoid content in hydroalcohlic extract was found to be 1.65 and 1.23% w/w.

Effect of *F. palmata* on Normoglycaemic Rats

Results of the effect of graded doses of *F. palmata* on blood glucose level of normal healthy rats are presented in Figure 1. The extract at doses of 50, 100 and 200 mg kg^{-1} produced significant ($P < 0.05$) dose-dependent blood glucose reduction with inhibition of 15.44%, 26.72% and 28.2%, respectively. Peak hypoglycaemic effect was observed at 3 h. Blood glucose levels were restored to normal in all treatment groups by 4 h.

Effect of *F. palmata* on Oral Glucose Tolerance in Normal Rats

The rats were divided into four groups of six animals each. Group I served as control; Group II, III and IV served as *F. palmata* test extract at different doses. The rats were fasted for 18 h and the test performed by oral administration of glucose (2 g kg^{-1}) to diabetic and normal rats 30 min

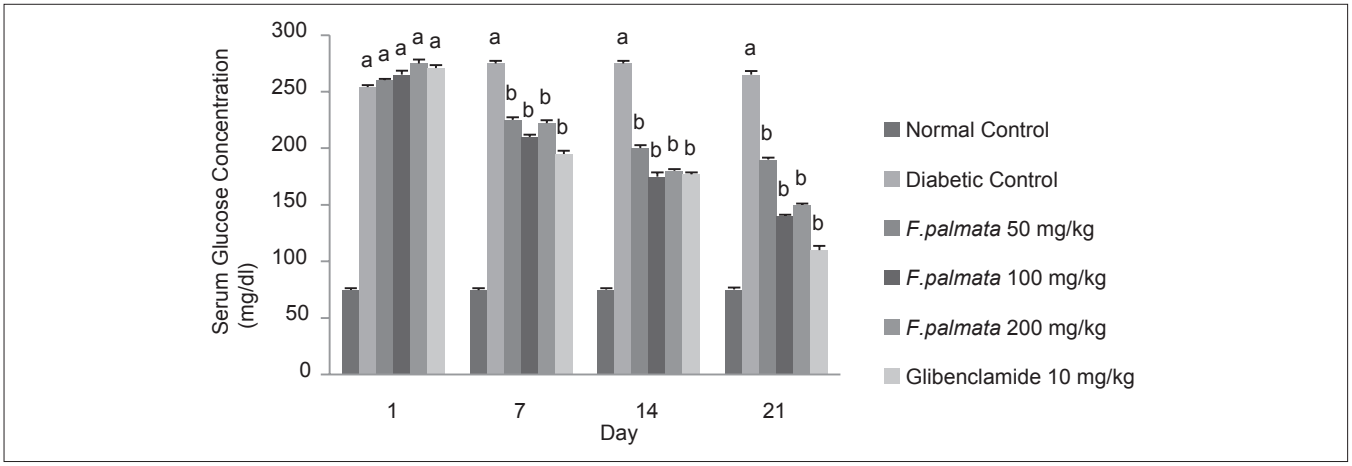

Figure 3: Effect of *F. palmata* on blood glucose levels of STZ-induced diabetic rats. Each value is expressed as mean ± S.E.M. ($n = 6$). $^{a}P < 0.001$ when compared to corresponding values of the normal control. $^{b}P < 0.001$ when compared to corresponding values of the diabetic control

after dosing. Blood samples were collected from the tail vein (under light ether anaesthesia) immediately 0, 30, 60, 90 and 120 min after the glucose administration and the blood glucose levels were estimated. The extract at doses of 50, 100 and 200 mg kg^{-1} produced 15.04%, 22.15% and 16.36% reduction in blood glucose level, respectively, when compared to vehicle-treated group at 60 min [Figure 2].

Effect of *F. palmata* on Fasting Blood Glucose and Body Weight in STZ-induced Diabetic Rats

The effect of repeated oral administration of *F. palmata* on blood glucose levels in STZ- diabetic rats is presented in Figure 3. *F. palmata* administered at doses of 50, 100 and 200 mg kg^{-1} to STZ-treated diabetic rats caused significant ($P < 0.001$) reduction of blood glucose levels which was related to dose and duration of treatment. Maximum reduction was observed on day 21 with inhibition values of 30.56%, 51.65% and 50.58%, respectively. Glibenclamide exhibited a 63.66% reduction in blood glucose levels at the end of the study when compared to diabetic control. STZ produced significant loss in body weight as compared to normal animals during the study. Diabetic control continued to lose weight till the end of the study while *F. palmata* at all the three doses (50, 100 and 200 mg kg^{-1}) showed significant improvement ($P < 0.05$) in body weight compared to diabetic control [Figures 3 and 4].

Effect of *F. palmata* on Serum Insulin in STZ-induced Diabetic Rats STZ Caused a Significant Decrease in Serum Insulin Compared to the Normal Control

Administration of *F. palmata* at all the three doses (50, 100 and 200 mg kg^{-1}) caused significant ($P < 0.01$) increase in insulin levels at the end of the study compared to the diabetic control group. Of the three doses, 100 mg kg^{-1} showed the greatest increase which was comparable to glibenclamide [Table 1].

Effect of *F. palmata* on Serum Lipids in STZ-induced Diabetic Rats

F. palmata showed a dose-related significant ($P < 0.01$) reduction in triglycerides with inhibition values of 15.91%,

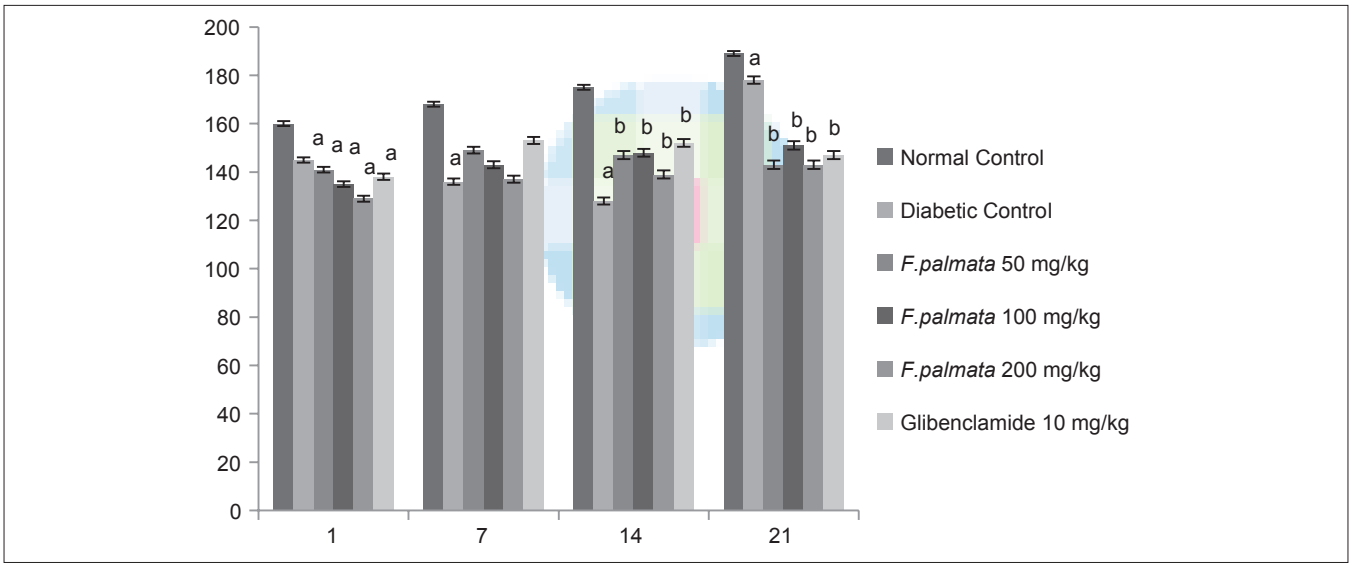

Figure 4: Effect of *F. palmata* on body weight of STZ-induced diabetic rats. Each value is expressed as mean ± S.E.M. ($n = 6$). [a]$P < 0.05$ when compared to corresponding values of the normal control. [b]$P < 0.05$ when compared to corresponding values of the diabetic control

Table 1: Effect of *F. palmata* on serum insulin, serum lipid and glycogen content in liver and skeletal muscle and lipid peroxidation in pancreases of STZ-treated diabetic rats

Exp. group	Serum insulin (µl/ml)*		Triglyceride (mg/dl)*		Total cholesterol (mg/dl)*		Glycogen (mg/g of wet tissue)*		TBARS (µm/g of wet tissue)*
	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21	Liver	Skeletal muscles	
Normal control	20.32±0.6	20.59±0.57	80±2.4	91.78±4.03	54±1.3	70±0.8	43±1.4	8.0±0.3	0.38±0.01
Diabetic control	9.68±0.14	7.14±0.3	162±0.3	221±1.6	97±2.3	140±2.4	16±1.9[d]	4.0±0.7[d]	0.67±0.02[d]
Diabetic-*F. palmata* 50 mg/kg	9.30±0.19	11.91±0.41[a,c]	174±1.4	150±2[a,c]	99±0.09	89±1.5	23±1.3	5.1±0.6	0.56±0.01
Diabetic-*F. palmata* 100 mg/kg	9.01±0.43	16.19±0.51[a,c]	177±2.03	139±3.1[a,c]	101±0.4	59±0.8[b,c]	29±1.6[c]	5.3±0.3[c]	0.48±0.01[c]
Diabetic-*F. palmata* 200 mg/kg	8.45±0.45	14.19±0.4[a,c]	163±1.9	129±2.4[a,c]	104±1.7	63±0.9[b,c]	30±1.1[c]	5.4±0.8[c]	0.43±0.01[c]
Diabetic+glibenclamide	8.16±0.45	18.49±0.9[a,c]	167±0.5	102±0.8[a,c]	99±1.6	54±0.5[b,c]	34±1.4[c]	4.8±0.3[c]	0.48±0.05[c]

*Each value is mean±SEM (n=6), [a]P<0.01 When compared to the day 1 value of same group, [b]P<0.001 When compared to the day 1 value of the same group, [c]P<0.001 When compared to the day corresponding value of the diabetic control, [d]P<0.001 When compared to the day corresponding value of the normal control, STZ – Streptozotocin; TBARS – Thiobarbituric acid reactive substance

24.62% and 27.11% for 50, 100 and 200 mg kg^{-1}, respectively, compared to pretreatment levels [Table 1]. *F. palmata* at the doses of 100 and 200 mg kg^{-1} was more effective than 50 mg kg^{-1} in reducing the cholesterol levels.

Effect of *F. palmata* on Glycogen Content in STZ-induced Diabetic Rats

Glycogen content in liver and skeletal muscle decreased significantly ($P < 0.001$) in diabetic control compared to normal control [Table 1]. Administration of *F. palmata* at doses of 100 and 200 mg kg^{-1} for 21 days resulted in significant ($P < 0.001$) increase in the glycogen levels in both the liver and skeletal muscle.

Effect of *F. palmata* on Pancreatic Lipid Peroxidation in STZ-induced Diabetic Rats

There was a significant elevation in the level of TBARS in the diabetic control when compared with the corresponding normal control. The oral administration of *F. palmata* and glibenclamide returned the values back to normal [Table 1].

Acute Oral Toxicity Study

In acute toxicity study, *F. palmata* did not elicit any mortality and treated animals did not show any change in their behavioural pattern. There was no significant difference in the body weights and food consumption when compared to the vehicle-treated group. Also, no gross pathological changes were seen. The extract at the dose of 2000 mg kg^{-1} did not elicit any mortality or visible signs of toxicity.

DISCUSSION

Oxidative stress is suggested to be a potential contributor to the development of complications in diabetes.[27] Increased free radical production or reduced antioxidant defense responses, both of which occur in the diabetic state may give rise to increased oxidative stress.[24] Consequences of oxidative stress are adaptation or cell injury i.e. damage to DNA, proteins and lipids, disruption in cellular homeostasis and accumulation of damaged molecules.[28] Reduced oxidative stress in the diabetic condition has been observed in experimental animals after the administration of certain polyphenols.

This study was undertaken to evaluate the hypoglycaemic activity of *F. palmata* in normal, glucose-loaded hyperglycaemic and streptozotocin-induced diabetic rats. In normoglycaemic rats, *F. palmata* showed dose-dependent hypoglycaemic effect at 3 h. The observed reduction in blood glucose was statistically significant with the administration of 100 and 200 mg kg^{-1} of the extract. In the OGTT, the extract at the dose of 100 mg kg^{-1} showed the greatest improvement in glucose tolerance. STZ significantly induced hyperglycaemia accompanied by hypoinsulinaemia. *F. palmata* at the dose of 100 mg kg^{-1} exhibited maximum glucose-lowering effect (51.65%) in diabetic rats and Glibenclamide exhibited 63.66% reduction in blood glucose level at the end of study when compared to diabetic control. *F. palmata* at the dose of 100 mg kg^{-1} increase the insulin level which was comparable to glibenclamide. Oral administration of *F. palmata* for 21 days caused a significant decrease in blood glucose levels. The possible mechanism by which *F. palmata* mediated its anti-diabetic effect may be due to potentiating of pancreatic secretion of insulin from existing β-cells of Islets of Langerhans as was evident by the significant increase in the level of insulin in the extract-treated animals. The hypoglycaemic activity of *F. palmata* was compared with glibenclamide.

Diabetes mellitus impairs the normal capacity of the liver to synthesise glycogen. Synthase phosphatase activates glycogen synthase resulting in glycogenesis and this activation appears to be defective in diabetes.[29] Skeletal muscle is also a major site of insulin-stimulated glucose uptake.[30] Decrease in both muscle and hepatic glycogen was observed in the diabetic group in this study. Treatment with *F. palmata* (100 and 200 mg kg^{-1}) for 21 days significantly increased muscle and liver glycogen indicating that the defective glycogen storage of the diabetic state was corrected by the extract. Hypercholesteraemia and hypertriglyceridaemia are primary factors involved in the development of atherosclerosis and coronary heart disease which are the secondary complications of diabetes.[31] *F. palmata* significantly reduced serum triglycerides and total cholesterol in STZ-diabetic rats suggesting that the extract modulated blood lipid abnormalities. In diabetes, tissue damage is considered to be mediated by free radicals by attacking membranes through peroxidation of unsaturated fatty acids.[32] Lipid peroxidation eventually leads to extensive membrane damage and dysfunction.[33] Decreased lipid peroxidation and improved antioxidant status may be one of the mechanism by which drug treatment could contribute to the prevention of diabetic complications.[34] In our study, *F. palmata* significantly attenuated the increased lipid peroxidation observed in the diabetic group. This could be due to the antioxidant effect of flavonoids and triterpenoids detected in the preliminary phytochemical screening of the extract.

Flavonoids by its ability to scavenge free radicals and due to inhibit lipid peroxidation prevents sterptozotocin-induced oxidative stress and decreased blood glucose levels thereby, potentiating the existing β-cells of the Islets of Langerhans in diabetic rats.[4]

Lipid peroxidation is a free-radical mediated propagation of oxidative insult to polyunsaturated fatty acids involving several types of free radicals and termination occurs through enzymatic means or by free radical scavenging by antioxidants.[35] Lipid peroxidation end products

measured as thiobarbituric acid reactive substances and hydroperoxides. Drugs with antioxidant properties may supply endogenous defense systems and reduce both initiation and propagation of reactive oxygen species.[36] Flavonoids effectively reduced the increased levels of thiobarbituric acid reactive substances and hydroperoxides in diabetic rats.

The anti-hyperglycaemic and lipid-lowering activity of *F. palmata* could be attributed to presence of β-sitosterol, sigmasterol, α-amyrin, β-amyrin and lupeol acetate. β-sitosterol reduce blood level of cholesterol and used in treating hypercholesterolaemia. β-sitosterol inhibits cholesterol absorption in the intestine.[37] Stigmasterol possesses potent antioxidant, hypoglycaemic and thyroid-inhibiting properties.[38] α-amyrin and β-amyrin both possesses anti-hyperglycaemic effect and hypolipidemic effects.[39] So future investigation therefore needs to be carried out on the plant to isolate the actual hypoglycaemic agents.

CONCLUSIONS

From this study, we can conclude that the hydroalcoholic extract of *Ficus palmata* Forsk leaves has beneficial effects on blood glucose level. It has the potential to impart therapeutic effect in diabetes and it may be a good alternative in the treatment of diabetes mellitus. The further investigation therefore needs to be carried out on the plant to isolate the active components. More study also needs to be done to establish the mechanism involved in the observed activities.

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