

Antihyperglycemic Activity of *Ficus glomerata* Stem Bark in Streptozotocin-Induced Diabetic Rats

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Abstract: The present investigation evaluated the antihyperglycemic activity of the bark powder and aqueous extract of *Ficus glomerata* (Moraceae) in streptozotocin induced diabetic rats. Oral administration of bark powder (FGB) and aqueous extract (FGAE) at 500 mg/kg caused 21% and 52% reduction in fasting blood glucose, respectively and also decreased glycosuria significantly. Histology of pancreas suggested normalization of islets of Langerhans and β -cells with respect to their number and cellular architecture. The results suggest that, the bark of *Ficus glomerata* has significant antihyperglycemic activity in experimental animals and has potential to be used as an adjunct in the management of diabetes mellitus.

Key words: *Ficus glomerata* • Antihyperglycemic • Islets of Langerhans • Streptozotocin • Blood glucose

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder affecting approximately 5% of the world's population. It is characterized by dysregulation in carbohydrate, protein and fat metabolisms caused by the complete or relative insufficiency of insulin secretion and/or insulin action [1]. Medicinal plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager [2]. *Ficus glomerata* Roxb. (Moraceae) commonly known as 'cluster fig' found throughout greater part of India in moist localities is widely used in Indian folk medicine for the treatment of diabetes mellitus [3]. All parts of this plant (leaves, fruits, bark, latex and sap of the root) are medicinally important in the traditional systems of medicine and have been used extensively in biliary disorders, jaundice, dysentery, diabetes, diarrhoea and as an anti-inflammatory agent. The bark, root and fruit have been found to possess antidiabetic activity. Reports indicate that the bark is antiseptic, antipyretic and vermifugal and bark decoction is used in treating various skin diseases and ulcers. It is used as a poultice in inflammatory swellings/boils. It is also valued to be effective in the treatment of hemorrhoids, dysentery, asthma, gonorrhoea, gleet, menorrhagia, leucorrhoea, hemoptysis and urinary diseases. The astringent nature of the bark has been employed as a mouth wash in spongy gum and also internally in dysentery,

Menorrhagia and haemoptysis [4-6]. Apart from the usage in traditional medicine, scientific studies indicate *F. glomerata* to possess various biological effects such as hepatoprotective [7], anti-inflammatory [8], antipyretic [9], antitussive [10] and antidiuretic [11].

Several mechanisms have been proposed for the hypoglycemic effect of phytochemicals, such as inhibition of carbohydrate metabolizing enzymes, manipulation of glucose transporters, β -cell regeneration and enhancing insulin releasing activity [12]. With this background, the present study was planned to explore the antihyperglycemic potential of the stem bark powder and aqueous extract of *F. glomerata* in diabetic rats.

MATERIALS AND METHODS

Plant Material: *Ficus glomerata* Roxb. stem bark was collected from Mukkadahally, Chamara Nagar district of Karnataka, India and subsequently a voucher specimen (BOT-001/2008) was deposited at the herbarium of Botany Department, University of Mysore. The bark was dried at 50°C, powdered, passed through 60 mesh sieve (BS) and stored in an air tight container at 4°C till further use.

Preparation of the Aqueous Extract: Aqueous extract was prepared by extracting the bark powder with hot water (70°C) in a mechanical shaker (24 h), filtered and freeze dried to obtain a dry extract powder (yield: 12% w/w).

Animals: Healthy adult male Wistar albino rats between 8-9 weeks of age and weighing 140-160 g were obtained from Central animal house, Dept of Zoology, University of Mysore. The rats were housed individually in metal cages, maintained under standard conditions (12 h photo period; $27\pm 2^\circ\text{C}$; $55\pm 5\%$ RH). The animals were maintained on standard laboratory diet consisting of wheat flour (62%), soy flour (18%), sugar (7%), mineral mixture (2%), vitamin mixture (1%) and groundnut oil (1%) corresponding to 60% carbohydrates, 30% protein, 5% fat and 5% fiber. All animal procedures have been approved by the Animal Ethical Committee in accordance with animal experimentation and care.

Streptozotocin Induced Hyperglycemia: The rats were divided into 1 control (non-diabetic rats) and 3 experimental groups namely, DC: untreated diabetic rats, FGB: *F. glomerata* bark powder treated diabetic rats and FGAE: aqueous extract treated diabetic rats. Diabetes was induced in experimental groups by a single intramuscular injection of streptozotocin (55 mg/kg body weight) after 24 h of fasting. Rats with fasting blood glucose more than 250 mg/dl were selected for the study. *F. glomerata* bark powder and aqueous extract at a level of 500 mg/kg body weight was mixed with the diet. The animals were maintained with the above treatment for a period of 15 days. During the study period, food and water intake of the rats were monitored and expressed as g/ml intake/week \pm SD. The rats were weighed once a week and the mean weights were calculated. Blood was collected from the retro-orbital plexus once a week and blood glucose was estimated by glucose oxidase peroxidase kit (Span diagnostics, India). Urine sugar was estimated by dipsticks (Rapha diagnostics, India).

Histo-Pathological Procedures: After 15 days rats were sacrificed under anesthesia, pancreas were immediately excised and fixed in a 10% solution of formaldehyde and then dehydrated in graduated ethanol (50-100%), cleared in xylene and embedded in paraffin. The hepatic sections (4-5 μm) were examined with a photomicroscope (40x) after staining with haematoxylin and eosin (H-E) dye. The histopathological studies were carried out at Ravi Diagnostic Laboratory, Mysore, India.

Statistical Analysis: The data on body weight, food intake, water intake, blood glucose and urine sugar is expressed as mean \pm SD. The data was analyzed by ANOVA followed by Tukey's test for significant differences using SPSS 14.0 computer software. The values were considered significant at $p \leq 0.05$.

RESULTS

Effect of FGB and FGAE on Body Weights: The data on mean body weights of the rats is given in Table 1. In control group, there was a steady increase in body weight (15% & 11% during first and second week respectively) while, in the experimental groups there was a loss of weight during the first week after induction of diabetes which continued in DC group. However, in FGB & FGAE treated rats a marginal increase in body weights was observed in the second week. No significant differences were observed in the body weights of control and experimental groups in the first but in the second week, the body weights of experimental groups were significantly lower than those of the control group.

Effect of FGB and FGAE on Food and Water Intake: During the first week, food intake was significantly higher in control group than the experimental groups but during the second week no significant differences were observed in the food consumption of various groups. The average water intake during the study period was significantly higher in the experimental groups compared to control group (Table. 2).

Table 1: Effect of *Ficus glomerata* bark powder and aqueous extract on body weights

Groups	Body weight in g*		
	Initial	1 st week	2 nd week
Control	145 \pm 17.2 ^a	166 \pm 18.9 ^a	184 \pm 9.9 ^a
FGB	152 \pm 26.5 ^a	137 \pm 21.6 ^a	137 \pm 13.4 ^b
FGAE	157 \pm 24.6 ^a	145 \pm 16.8 ^a	150 \pm 15.6 ^b
DC	155 \pm 19.1 ^a	140 \pm 15.9 ^a	125 \pm 17.1 ^b

*values are mean \pm SD

[§]FGB: *F. glomerata* bark powder, FGAE: Aqueous extract of *F. glomerata* bark.

**Mean values carrying different superscript letters a, b, c,....., in columns differ significantly ($p \leq 0.05$).

Table 2: Effect of *Ficus glomerata* bark powder and aqueous extract on food intake & water intake

Groups	Food intake (g)		Water intake(ml)	
	1 st week	2 nd week	1 st week	2 nd week
Control	67.8 \pm 7.7 ^b	69.5 \pm 4.1 ^a	160 \pm 21.9 ^a	163 \pm 25.8 ^a
FGB	44.2 \pm 4.1 ^b	80.2 \pm 9.0 ^b	262 \pm 16.4 ^b	262 \pm 16.4 ^b
FGAE	50 \pm 10.8 ^a	76.4 \pm 15.0 ^b	270 \pm 27.4 ^b	234 \pm 18.2 ^b
DC	51 \pm 5.7 ^b	85 \pm 10.3 ^b	267 \pm 20.1 ^b	283 \pm 15.7 ^b

*values are mean \pm SD

[§]Mean values carrying different superscript letters a, b, c,....., in columns differ significantly ($p \leq 0.05$)

Table 3: Effect of *Ficus glomerata* bark powder and aqueous extract on blood glucose

Groups	Blood glucose mg/dl		
	Initial	1 st week	2 nd week
Control	82 ± 11.34 ^a (1 ± 0.0)	84 ± 8.2 ^a (1 ± 0.0)	72 ± 9.00 ^a (1 ± 0.0)
FGB	362 ± 23.1 ^b (3.8 ± 0.4)	289 ± 22.6 ^c (2.2 ± 0.8)	285 ± 29.5 ^c (1.6 ± 0.5)
FGAE	347 ± 22.4 ^b (3.6 ± 0.5)	172 ± 6.15 ^b (2.0 ± 0.4)	168 ± 9.12 ^b (1.0 ± 0.0)
DC	365 ± 19.3 ^b (3.8 ± 0.4)	459 ± 21.6 ^d (4.0 ± 0.0)	475 ± 25.1 ^d (4.0 ± 0.0)

*Values are mean ± SD

**Mean values carrying different superscript letters a, b, c,....., in rows differ significantly (p < 0.05).

§Values in parenthesis represent % urine sugar 1: Nil, 2: Traces, 3:1%, 4: >2%.

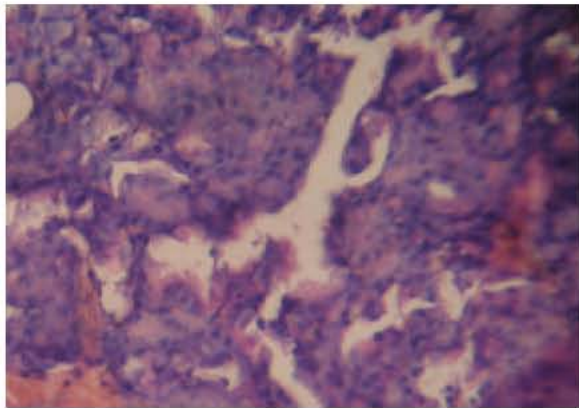


Fig. 1: Section of pancreas from normal rats showing normal pancreatic architecture

Effect of FGB and FGAE on Blood Glucose: *F. glomerata* bark powder caused 20% reduction in the blood glucose during the first week followed by a reduction of 21% in the 2nd week (Table. 3). The blood glucose decreased from the initial level of 362 mg/dl to 285 mg/dl during the 2nd week. The aqueous extract of *F. glomerata* bark showed better hypoglycemic activity wherein, the blood glucose decreased from an initial level of 347 mg/dl to 168 mg/dl after 15 days. The percent reduction in blood glucose was 50% and 52% for the first and second week respectively. In untreated diabetic rats blood glucose increased from 365 to 475 mg/dl by the end of the study period. Initial urine sugar was >2% in the experimental groups which later decreased to traces in FGB group and was undetected in FGAE group in the second week while, it was >2% in DC group.

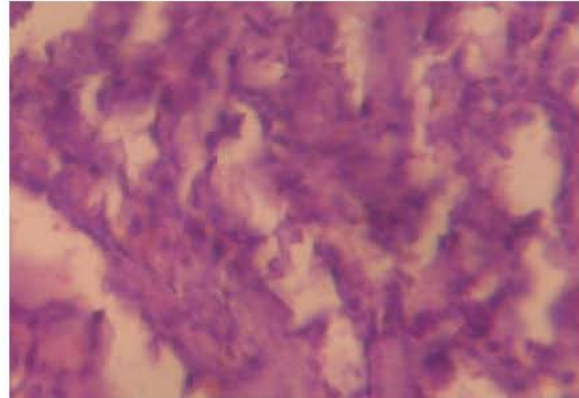


Fig. 2: Section of pancreas from untreated diabetic rats (DC) showing reduced number of pancreatic cells

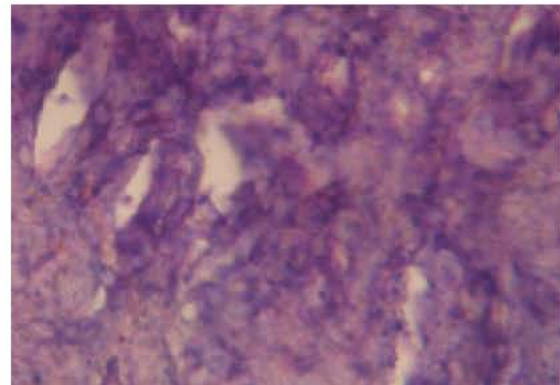


Fig. 3: Section of pancreas from FGB group rats showing slight increase in number of pancreatic cells

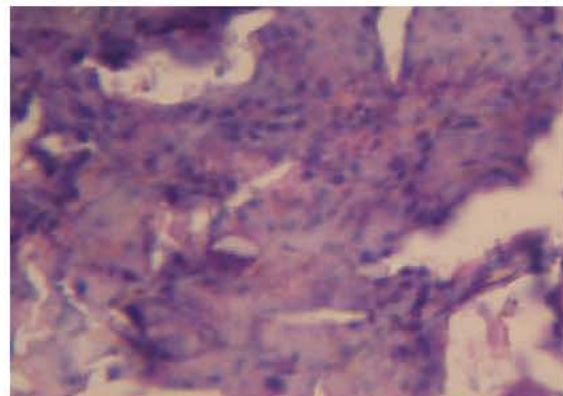


Fig. 4: Section of pancreas from FGAE group rats showing normalization of pancreatic architecture

Effect of FGB and FGAE on Histology of Pancreas: Administration of STZ decreased the number of β-cells and the sections from untreated diabetic group (DC) demonstrated shrunken islets of Langerhans with degenerative necrosis (Fig. 2). In the sections from FGB

and FGAE treated rats, islets of Langerhans appeared less shrunken compared to those from the untreated group (Fig. 3-4). FGAE showed higher number of normal islets of Langerhans than FGB treated rats. The FGE and FGAE groups demonstrated lesser number of β -cells compared to sections from those of the control group (Fig. 1).

DISCUSSION

The present study evaluated the antihyperglycemic activity of *F. glomerata* bark powder and aqueous extract in streptozotocin induced diabetic rats. STZ-induced diabetic rats have been widely used as a model for evaluation of antidiabetic activity. The fundamental mechanism underlying hyperglycemia in diabetes mellitus involves over-production (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues [13]. The diabetes induced by STZ is associated with polydipsia and loss of body weight. FGB and FGAE decreased the water consumption to near normal levels indicating normalization of blood glucose levels. Furthermore, food intake of FGAE group was comparable to that of control group. Diabetic rats treated with FGB and FGAE showed an increase in body weight as compared to the diabetic control (DC), which may be due to its protective effect in controlling muscle wasting i.e. reversal of gluconeogenesis and may also be due to the improvement in glycemic control. Similar observations are reported by other authors for some other plant extracts [14-15].

Our investigations indicate the efficiency of *F. glomerata* in the maintenance of blood glucose levels in streptozotocin induced diabetic rats. Administration of FGB and FGAE to diabetic rats showed a significant decrease in the levels of blood glucose. The possible mechanism by which *F. glomerata* brings about its antihyperglycemic action in diabetic rats may be by potentiating the insulin effect of plasma by increasing either the pancreatic secretion of insulin from the existing β -cells or by its release from the bound form. The histopathological observation confirms this phenomenon where, damage caused by STZ was partially reversed and the pancreatic architecture restored towards normalization. The antihyperglycemic property of *F. glomerata* could be attributed to the presence of β -sitosterol, stigmaterol, β -amyrin, lupeol acetate [16], leucocyanidin-3-O- β -D-glucopyranoside, leucopelargonidin-3-O- β -D-glucopyranoside and leucopelargonidin-3-O- α -L-rhamnopyranoside [17] reported to exhibit antidiabetic and inhibitory effects on the enzymes of carbohydrate metabolism.

The antihyperglycemic higher effect of FGAE was superior to that of leucopelargonidin derivative isolated from *Ficus bengalensis* which decreased fasting blood glucose to an extent of 34% at a dosage level of 100 mg/kg in diabetic rats [18]. However, the antihyperglycemic effect of FGAE was similar to that of leucopelargonidin (250 mg/kg) and glibenclamide (2 mg/kg), an oral hypoglycemic agent [19]. Although STZ is reported to cause rapid and irreversible necrosis of pancreatic β -cells, administration of alkaloid extract of *Ephedra distachya* herbs and L-ephedrine is reported to regenerate functioning pancreatic islet cells as well as those that were atrophic [20] suggesting differentiation and proliferation of residual pancreatic β -cells. These reports support the histopathological observations wherein, both the number and structural integrity of islets of Langerhans were restored towards normalization. This phenomenon could lead to an increase in insulin synthesis and secretion thereby correcting the diabetic state.

In conclusion, the results of the present study planned as a preliminary screening of *Ficus glomerata* bark suggests that, the antihyperglycemic effect of the aqueous extract was superior to that of the bark powder as such and the compound(s) of potential antihyperglycemic effect is/are extractable in the water which makes it easier and appropriate for possible human consumption. The antihyperglycemic efficacy may be even higher after purification of the compound(s). Further studies in this direction are currently in progress.

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