



Glucose-lowering, Hepatoprotective and Hypolipidemic Activities of Stem Bark of *Ficus racemosa* in Streptozotocin-Induced Diabetic Rats

Ahmed F, Urooj A

Department of Studies in Food Science and Nutrition, University of Mysore, Mysore-570 006, India

Address for correspondence: Dr. Faiyaz Ahmed; E-mail: fayaz_ahmed09@yahoo.co.in

ABSTRACT

The present study evaluated the antihyperglycemic, hepatoprotective, and hypolipidemic effects of *F. racemosa* bark powder and aqueous extract in streptozotocin-induced diabetic rats. Streptozotocin-induced diabetic rats ($n = 6$) were treated with *F. racemosa* Linn (Moraceae) bark powder (FRP) and aqueous extract (FRAE) for six weeks. Blood glucose was determined every 15 days using a portable glucometer. At the end of the study period, the rats were sacrificed and levels of serum glucose, protein, total cholesterol, triglycerides, AST, ALT, TBARS, and glutathione were determined as indicators of antihyperglycemic, hypolipidemic, and hepatoprotective activities, as well as of antioxidant potential. TBARS and glutathione levels were determined in the liver and the kidneys also. Both the bark powder and aqueous extract of *F. racemosa* bark caused a significant reduction ($P \leq 0.05$) in blood glucose (54 and 66% respectively). A significant reduction ($P \leq 0.05$) was also observed in serum cholesterol and triglyceride levels to the control levels. The aqueous extract was more effective and caused a significant reduction ($P \leq 0.05$) in TBARS, AST, ALT levels compared to untreated diabetic rats. However, it did not reach control levels. A significant increase in glutathione concentrations over the control levels was also observed in rats treated with *F. racemosa* bark. It is concluded that *F. racemosa* bark has a significant hypolipidemic and hepatoprotective effect besides being a potent antihyperglycemic agent.

Key words: Antihyperglycemic, antioxidant effect, *Ficus racemosa*, hypolipidemic, hepatoprotective

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INTRODUCTION

Several members of the genus *Ficus* (Moraceae) are being used traditionally in a wide variety of ethnomedical remedies. One among them, *Ficus racemosa* Linn., syn. *Ficus glomerata* Roxb., commonly known as 'Gular', 'Umbar,' or 'Jagyadumbar,'^[1,2] is widely distributed all over India, northern Australia, and other parts of Asia. All parts of this plant are medicinally important in the traditional system of medicine in India and have been used extensively in biliary disorders, jaundice, dysentery, diabetes, diarrhea, and in inflammatory conditions.^[3-5] The stem bark of the tree is employed in the indigenous systems

of medicine for a variety of purposes, including coughs and colds.^[5] The bark is astringent, antiseptic, antipyretic, and vermifugal. An infusion of the bark is employed as a mouthwash for spongy gum condition, and the decoction is used for treating various skin diseases and ulcers. It is used as a poultice in inflammatory swellings and boils. It is also reported to be effective in the treatment of piles, dysentery, asthma, gonorrhoea, gleet, menorrhagia, leucorrhoea and hemoptysis, and urinary diseases.^[1,3,4] Reports indicate that *F. racemosa* possesses various biological activities such as hepatoprotective, chemopreventive, antidiabetic, anti-inflammatory, antipyretic, antitussive, antidiarrhoeal, and antidiuretic activities.^[6-13]

In view of the above knowledge, the present study was planned to explore the glucose-lowering, hepatoprotective, and hypolipidemic potential of *F. racemosa* bark powder and aqueous extract in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Collection of plant material

Ficus racemosa Linn. stem bark was collected from Mukkadahally, Chamarajanagar district of Karnataka, India, and a voucher specimen was subsequently deposited at the herbarium of Department of Studies in Botany, University of Mysore, Mysore (BOT-001/2008).

Preparation of aqueous extract

The bark was cut into small pieces, spread over filter sheets, and dried overnight in a vacuum oven at 50°C. The dried pieces were ground to a fine powder in a dry grinder, passed through 60 mesh sieve (BS) and stored in an airtight container at 4°C until further use. A weighed quantity (100 g) of this powder was taken into a conical flask containing 800 mL distilled water and extracted using a temperature-controlled mechanical shaker at 70°C for 24 h. The extract was filtered and freeze-dried (yield: 12% w/w).

Animals

Healthy adult male Wistar rats between eight and nine weeks of age and weighing 140-160 g were obtained from the Central animal house, Department of Zoology, University of Mysore. The rats were housed individually in metal cages, maintained under standard conditions (12 h light and 12 h dark cycles; 27±2°C; 45-60% humidity). The animals were fed a standard 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 and were provided with food and water *adlibitum*. All animal procedures have been approved by the Animal Ethical Committee of the University of Mysore.

Experimental design and induction of diabetes

The rats were assigned to six groups ($n = 6$), control group: nondiabetic rats, FRP group: *Ficus racemosa* powder-treated diabetic rats, FRAE group: *Ficus racemosa* aqueous extract-treated diabetic rats, DC group: Untreated diabetic rats, GB group: Glibenclamide-treated diabetic rats (400 µg/day/kg body weight),^[14] IN group: Insulin-treated diabetic rats (5 U/day/kg).^[14] Diabetes was induced in the

experimental groups by a single intramuscular injection of streptozotocin (55 mg/kg, Sigma Aldrich, India) dissolved in citrate buffer (0.1 M, pH 4.5) after 24 h of fasting.^[15] Hyperglycemia was confirmed by elevated blood glucose levels after 72 h and rats with fasting blood glucose > 250 mg/dL were selected for the study. The powder and aqueous extract were mixed at dose levels of 500 mg/kg body weight with the diets of the respective experimental groups. The animals were maintained for six weeks with the above treatment.

Assay of biochemical parameters

Blood glucose levels were estimated using a glucometer (Accu-chek, Roche Diagnostics, Germany) every 15 days. At the end of the study period, rats were decapitated, blood samples were collected by direct cardiac puncture, centrifuged at 2500 *g* for 20 min, and used for the assay of the following biochemical parameters using diagnostic kits from Agappe Diagnostics, India: Total protein (No. 11013001), albumin (No. 11001001), total cholesterol (No. 11204001), triglycerides (No. 11215001), aspartate aminotransferase (AST, No. 11213001), and alanine aminotransferase (ALT, No. 11214001). The liver and kidneys were immediately excised, homogenized with phosphate-buffered saline (1:5 w/v, pH 7.4) in cold conditions, and used for the assay of TBARS according to the method of Ohkawa *et al.*^[16] and glutathione by the method of Ellman.^[17] TBARS and glutathione levels were also determined in serum.

Statistical analysis

The data was analyzed by ANOVA, followed by Tukey's multiple comparisons test for significant differences using SPSS 14.0 computer software. Values were considered to be significant at $P \leq 0.05$.

RESULTS

Changes in blood glucose of various groups are presented in Figure 1. FRP and FRAE caused a significant reduction ($P \leq 0.05$) of fasting blood glucose (54 and 66% respectively) but not to control levels. The antihyperglycemic effect of FRP and FRAE did not differ statistically ($P \leq 0.05$) with the antihyperglycemic effect of FRAE being comparable to that of glibenclamide. As expected, the standard antidiabetic agents, insulin and glibenclamide, reduced the fasting blood glucose levels to the control levels. The percent reduction brought about by insulin and glibenclamide were 78 and 74% respectively.

Serum cholesterol and triglyceride levels were significantly higher ($P \leq 0.05$) in the DC group compared to those of

the control group [Table 1]. Administration of FRP and FRAE caused a highly significant ($P \leq 0.01$) reduction in serum cholesterol and triglyceride levels comparable to those of the control group. Similar observations were also found with respect to the IN- and GB-treated groups where serum cholesterol and triglyceride levels were decreased to control levels. The total protein concentration was significantly lower ($P \leq 0.05$) in the DC group compared to that in the control group. However, no significant differences were observed in total protein concentrations of the FRP, FRAE, IN, and GB groups in comparison with that of the control group. STZ injection caused a highly significant reduction ($P \leq 0.05$) of serum albumin concentration in the DC group compared

to the control group. However, although administration of FRP and FRAE significantly restored albumin levels, control levels were not reached. Similar observations were seen in IN- and GB- treated groups.

The hepatoprotective activity of FRP and FRAE was assessed by measuring the activity of serum transaminases (AST and ALT). The results reveal that both FRP and FRAE caused a significant reduction ($P \leq 0.05$) in the activity of both ALT and AST compared to the activity found in untreated diabetic rats [Table 1].

Treatment of diabetic rats with FRP and FRAE resulted in a significant ($P \leq 0.05$) improvement in the antioxidant status, as evident by low TBARS and higher GSH levels in the serum, liver, and kidneys. TBARS concentrations were significantly higher ($P \leq 0.05$) in the serum, liver and kidneys of untreated animals than of the control group. The concentrations of GSH were significantly lower ($P \leq 0.05$) in untreated diabetic rats as well as the FRP-treated rats compared to control group. The concentrations of GSH in the liver and kidneys of FRP-treated animals were comparable to that of those in the FRAE group. However, administration of FRP and FRAE resulted in a significant increase ($P \leq 0.05$) in GSH levels compared to control and untreated diabetic rats [Table 2].

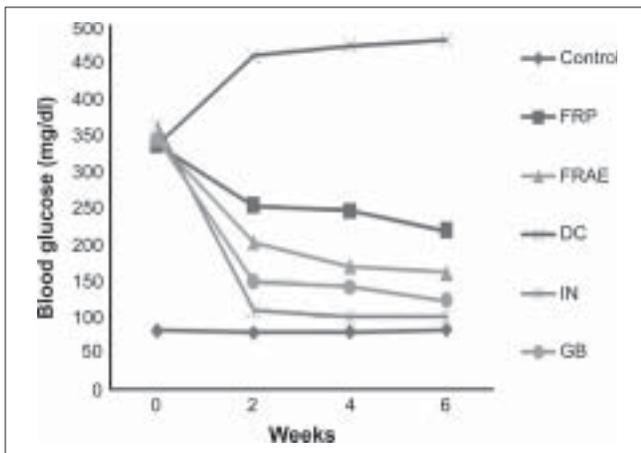


Figure 1: Effect of FRP and FRAE on blood glucose; *values are Mean \pm SD (n = 6) #control: Nondiabetic rats; FRP: *Ficus racemosa* bark powder-treated rats; FRAE: Aqueous extract-treated rats DC: Untreated diabetic rats; IN: Insulin-treated diabetic rats; GB: Glibenclamide-treated diabetic rats

DISCUSSION

Streptozotocin (STZ) is widely used to induce diabetes in experimental animals. As STZ is a nitric oxide (NO) donor and NO was found to bring about the destruction of

Table 1: Effects of *Ficus racemosa* bark and aqueous extract-treated rats on biochemical parameters in serum

| Group | Total protein g/dL | Albumin g/dL | Globulin g/dL | TC mg/dL | TGL mg/dL | AST U/L | ALT U/L |
|---------|------------------------------|---|------------------------------|----------------------------|------------------------------|-------------------------------|--|
| Control | 6.8 ^b \pm 1.00 | 4.6 ^c \pm 0.40 | 2.2 ^{ab} \pm 1.16 | 57 ^a \pm 7.23 | 104 ^a \pm 24.4 | 23.3 ^a \pm 2.3 | 6.3 ^a \pm 1.51 |
| FRP | 6.06 ^b \pm 0.18 | 3.5 ^b \pm 0.51 | 2.56 \pm 0.47 ^b | 57 ^a \pm 8.70 | 103 ^a \pm 4.80 | 63.0 ^c \pm 7.20 | 36.8 ^c \pm 2.90 |
| FRAE | 6.22 ^b \pm 0.76 | 3.74 ^b \pm 0.78 | 2.48 ^a \pm 0.45 | 55 ^a \pm 9.36 | 99 ^a \pm 10.8 | 48.8 ^b \pm 10.8 | 33.6 ^{bc} \pm 2.10 |
| DC | 5.40 ^a \pm 0.50 | 2.40 ^a \pm 0.26 ^a | 3.02 ^b \pm 0.58 | 100 ^b \pm 5.3 | 143 ^b \pm 17.9 | 156.6 ^d \pm 20.9 | 65.4 ^d \pm 9.1 ^c |
| IN | 6.09 ^b \pm 1.73 | 3.72 ^b \pm 0.14 | 2.37 ^a \pm 1.81 | 60 ^a \pm 8.28 | 117 ^a \pm 11.16 | 57.7 ^c \pm 5.73 | 32.8 ^b \pm 1.71 |
| GB | 6.07 ^a \pm 0.43 | 3.32 ^b \pm 0.66 | 2.69 ^a \pm 0.60 | 56 ^a \pm 5.34 | 97 ^a \pm 16.75 | 65.3 ^c \pm 7.51 | 35.4 ^c \pm 1.89 |

*Mean \pm SD carrying different superscript letters a, b, c,..... in columns differ significantly ($P \leq 0.05$); #Control: Nondiabetic rats; FRP: *Ficus racemosa* bark powder-treated rats; FRAE: Aqueous extract-treated rats; DC: Untreated diabetic rats; IN: Insulin-treated diabetic rats; GB: Glibenclamide-treated diabetic rats TC: Total cholesterol, TGL: Triglycerides

Table 2: Hepatoprotective and antioxidant activities of *Ficus racemosa* bark and Aqueous extract-treated rats

| Group | Serum | | Liver | | Kidney | |
|---------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| | TBARS nmoles/mg P | GSH μ m/mg P | TBARS n moles/mg P | GSH μ m/mg P | TBARS n moles/mg P | GSH μ m/mg P |
| Control | 0.08 ^a \pm 0.01 | 0.17 ^b \pm 0.06 | 0.05 ^a \pm 0.01 | 5.28 ^c \pm 0.26 | 0.07 ^a \pm 0.02 | 4.37 ^c \pm 0.98 |
| FRP | 0.16 ^b \pm 0.06 | 0.13 ^b \pm 0.02 | 0.34 ^c \pm 0.03 | 4.91 ^c \pm 0.55 | 1.20 ^c \pm 0.15 | 3.23 ^b \pm 0.93 |
| FRAE | 0.11 ^b \pm 0.06 | 0.16 ^b \pm 0.04 | 0.17 ^b \pm 0.03 | 5.15 ^c \pm 0.30 | 0.64 ^b \pm 0.06 | 3.84 ^c \pm 0.33 |
| DC | 0.29 ^c \pm 0.03 | 0.05 ^a \pm 0.01 | 0.43 ^d \pm 0.03 | 0.55 ^a \pm 0.10 | 1.84 ^d \pm 0.15 | 0.93 ^a \pm 0.07 |
| IN | 0.15 ^b \pm 0.02 | 0.17 ^b \pm 0.04 | 0.16 ^b \pm 0.01 | 3.91 ^b \pm 0.10 | 0.60 ^b \pm 0.03 | 4.24 ^c \pm 0.72 |
| GB | 0.21 ^c \pm 0.06 | 0.17 ^b \pm 0.03 | 0.21 ^b \pm 0.04 | 4.07 ^b \pm 0.39 | 0.62 ^b \pm 0.06 | 3.23 ^b \pm 0.49 |

*Values are mean \pm SD (n = 6) **values carrying different superscript letters a, b, c,..... in columns differ significantly ($P \leq 0.05$); #Control: Nondiabetic rats; FRP: *Ficus racemosa* bark powder-treated rats; FRAE: Aqueous extract-treated rats; DC: Untreated diabetic rats; IN: Insulin-treated diabetic rats; GB: Glibenclamide-treated diabetic rats; TBARS: Thiobarbituric acid reactive substances; GSH: Glutathione, mg p: Mg protein

pancreatic islet cells, NO has been proposed to contribute to STZ-induced DNA damage.^[18,19] STZ was also found to generate reactive oxygen species which contribute to DNA fragmentation and evoke deleterious changes in the cells.^[20,21] It has been suggested that some inhibitors of polyADP-ribosylation may also exert a protective effect due to their hydroxyl radical-scavenging properties.^[22] The present investigation studied the hypoglycemic and hypolipidemic potential as well as the ability of *F. racemosa* to counteract free radicals in STZ-induced diabetic rats.

The hypoglycemic effect of *F. racemosa* can be attributed to the presence of leucocyanidin-3-O- β -D-glucopyranoside, leucopelargonidin-3-O- β -D-glucopyranoside, leucopelargonidin-3-O- α -L-rhamnopyranoside,^[23] all of which are known to reduce hyperglycemia. These compounds are also isolated from *Ficus bengalensis* and the leucopelargonidin derivative isolated from *Ficus bengalensis* has been shown to decrease fasting blood sugar levels at a dosage level of 100 mg/kg/day in diabetic rats to 34% of the levels in untreated diabetic rats.^[24,25]

The levels of serum lipids are usually elevated in diabetes mellitus and such an elevation represents a risk factor for coronary heart disease. This abnormally high level of serum lipids is mainly due to the uninhibited actions of lipolytic hormones on the fat depots; thus, hypercholesterolemia and hypertriglyceridemia are known to occur in STZ-induced diabetic rats. Under normal circumstances, insulin activates the enzyme lipoprotein lipase, which hydrolyzes triglycerides. However, lipoprotein lipase is not activated in conditions of insulin deficiency, thus resulting in hypertriglyceridemia.^[28] The observed hypocholesterolemic and hypotriglyceridemic effects of *F. racemosa* bark can therefore be attributed to the activation of the enzyme, lipoprotein lipase.

A number of enzymes are synthesized by the liver and levels of some of these enzymes are commonly measured in the bloodstream to assess liver function. The reduction of AST and ALT caused by both FRP and FRAE reflects the hepatoprotective effect of *F. racemosa* bark as levels of transaminases, often referred to as AST and ALT, are found to be elevated as a result of hepatic damage/injury.^[28] Similar observations are reported by Subhash *et al.* where a petroleum ether extract of *F. racemosa* leaf caused a highly significant reduction of AST and ALT in rats treated with carbon tetrachloride (CCl₄).^[6]

The low TBARS and higher GSH levels in the serum, kidney, and liver of *F. racemosa*-treated groups represent its antioxidant potential. As the chemical composition

and medicinal uses of *F. racemosa* have been widely reported, the observed hepatoprotective and antioxidant effects could be attributed to the presence of the various phytoconstituents including tannins, kaempferol, rutin, bergapten, psoralenes, flavonoids, fucosin, coumarin, and phenolic glycosides^[26] that are reported to act as strong antioxidants and anti-inflammatory agents.^[7]

CONCLUSION

From the results of the present study, it can be concluded that *F. racemosa* bark is a potent antihyperglycemic, hypolipidemic, and hepatoprotective agent. Further, the aqueous extract was more effective than the bark powder, indicating the role of water-soluble phytoconstituents rather than the plant fiber for the observed biological effects. The biological efficacy of *F. racemosa* bark may be even higher after the isolation and purification of the compound(s). Further studies in this direction are currently in progress.

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