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Antihyperglycemic and hypoglycemic effect of *Ficus racemosa* leaves

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Abstract

Objective: To investigate the hypoglycemic and antihyperglycemic effects of an ethanolic extract of the leaves of *Ficus racemosa* in both normal and alloxan induced *diabetes* in rats. Materials and methods: Blood samples were collected from the retro-orbital plexus under light ether anesthesia before and at 0.5, 1, 2, 4, 6, 8 and12 h after the oral administration of 100, 200, and 300/kg doses. Blood glucose was analyzed by glucose-oxidase method using a visible spectrophotometer. Results: Graded doses of the alcoholic extract when given to both normal and diabetic rats produce significant reductions in blood glucose at the 6 h after ethanolic extract administration ($P < 0.001$). The effect was found to be dose dependent with all treatments at the doses administered. Conclusion: The present study clearly indicated a significant antidiabetic activity of the leaves of *Ficus racemosa* and supports the traditional usage of fruits by the Ayurvedic physicians for the control of *diabetes*.

Keywords: *Ficus racemosa*, blood glucose, alloxan, *diabetes* mellitus, rats.

1. Introduction

Diabetes mellitus is characterized by hyperglycemia together with biochemical alterations of glucose and lipid metabolism.1 Liver is an insulin dependent tissue, which plays a pivotal role in glucose and lipid homeostasis and is severely affected during *diabetes* [2] liver participates in the uptake, oxidation and metabolic conversion of free fatty acids, synthesis of cholesterol, phospholipids and triglycerides. During *diabetes* a profound alteration in the concentration and composition of lipid accurs [3]. Decreased glycolysis, impeded glycogenesis and increased gluconeogenesis are some of the changes of glucose metabolism in the diabetic liver [4]. Many traditional plant treatments for *diabetes* mellitus are used throughout the world [5] few of the traditional plant treatments for *diabetes* has received scientific scrutiny, and the World Health Organization has recommended that this area warrants attention [6].

In the present study attempts were made to study detail phytochemical and pharmacological, particularly anti-hyperglycemic activity of the leaves of *Ficus racemosa* belonging to family

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Moraceae. The root sap is used for treating *diabetes*; both the root and fruit are credited with hypoglycemic activity. The root juice is reportedly useful for treating dysentery. The stem bark is used to treat menorrhagia, leucorrhoea, gonorrhoea, urinary diseases, haemorrhage and skin diseases. Both the fruits and bark are used extensively in Ayurvedic and Unani medicine [7-8]. The following phytoconstituents have been isolated from the plant tannins, [9] leucoanthopcyanins, leucocyanidin-3-0-β-D-glucopyranoside and leucopelargonodine-3-0-α-L-rhamnopyrano-side, β-sitosterol, stigmasterol, lupeol,ceryl behenate, α-amyrin acetate [10].

Ficus racemosa documented to possessed anti-inflammatory [11-13], anti-pyretic [14], antidiuretic [15]. The bark of *Ficus racemosa* is reported to possess the Antidiabetic activity [16]. The bark and leaves of this group used as astringent, haemostatic, anti-inflammatory, antiseptic, prescribed in diarrhea, dysentery and in treatment of skin disease ulcers vaginal disorder leucorrhoea monorrhagia deficient lactation and act as urinary astringent and reduce sugar in diabetic [17]. Still no scientific study has been carried out on the leaves of this plant for *diabetes*. Our aim to evaluate efficacy of this plant in *diabetes* mellitus.

2. Materials and Methods

2.1 Plant Material

Fresh leaves of the plant were collected from our university campus, North Maharashtra University, Jalgaon, India. It was authenticated by Dr.P.S.N.Rao Joint Director from the Botanical Survey of India, Pune. Voucher No. is (VVP1) dated 09/11/2005. and letter No.BSI/WC/Tech/2005/728.

2.2 Preparation of the extract

Leaves were dried under normal environmental condition. The completely dried leaves were powdered with an electric grinder and used for the extraction. Since ethanol is the common solvent for extracting most of the constituents present in herbal material, the powdered leaves were extracted by percolation at room temperature with 80% ethyl alcohol. The extract was concentrated under reduced pressure (bath, temperature 50°C) and dried in a vacuum dessicator (yield 15% w/w). Samples were then suspended in 5% gum acacia at a concentration of 100mg/ml and used in all experiments. Preliminary phytochemical screening was carried out on the extract.

2.3 Animals

Normal healthy Albino rats (200-250 g) of Wistar strain of either sex obtained from Yash Farms, Pune were used in the study. They were divided in to 10 groups of five each and were provided with standard pellet diet (Goldmuhar Brand, Lipton India Ltd., Mumbai.) and water *ad libitum*. All the rats were kept in cages with wide square mesh at the bottom to avoid coprophogy and maintained in a well ventilated animal house with 12 h light and dark cycle. They were fasted for 18 h prior to the experiment, allowing access to water only, and were deprived of both food and water during the 12 h monitoring period of the experiment after the treatment either with the drug (or) vehicle. The experimental protocol and animal house has been approved by the institutional animal ethics committee and by the animal regulatory body of the Indian Government (Registration No.652/02/a/ CPCSEA, dated 25/01/1999).

2.4 Chemicals used

Glibenclamide was a generous gift sample from Themis laboratories wagle estate, Thane. Alloxan monohydrate was purchased from Sigma-Aldrich Himedia. The glucose oxidase/peroxidase reagents kit was purchased from Dr. Reddy's Laboratories Hyderabad. All other reagents used were of analytical grade.

Table 1. Effect of *Ficus racemosa* leaves extract on blood glucose levels after oral administration in normal rats.

Group (n=5)	Dose	Blood glucose levels at different hours after the treatment							
		0	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**
Control	-	111.05±4.10	109.70±3.10	108.08±3.00	108.75±2.42	108.65±1.90	109.58±0.99	108.50±1.90	109.21±2.50
F.racemosa	100mg/kg	110.56±2.10	108.35±3.40	105.92±3.56	101.27±2.57*	99.33±1.20**	87.74±5.25**	87.90±3.25***	98.62±4.10*
F.racemosa	200mg/kg	106.70±5.25	105.08±6.11	98.05±4.22	95.31±5.20	86.68±3.12*	81.16±2.94***	83.20±3.26***	91.70±1.90*
F.racemosa	300mg/kg	98.60±4.20	96.83±3.25	90.64±1.97	87.13±3.20*	78.80±4.91*	73.59±2.60***	75.40±0.5***	87.55±3.21*
Glibenclamide	10mg/kg	101.20±1.90	95.78±2.63	89.65±3.13*	86.57±2.93**	76.73±3.10***	71.40±4.06***	78.05±2.10***	90.25±3.52*

All blood glucose values were expressed as Mean ± S.E.M of five animals.

All blood glucose values were compared with corresponding values of control groups by using one way ANOVA dunett's test.

Statistical significant difference were expressed as *p<0.05, **p<0.01, ***p<0.001

Table 2. Effect of *Ficus racemosa* leaves extract on blood glucose levels after oral administration in diabetic rats.

Group (n=5)	Dose	Blood glucose levels at different hours after the treatment							
		0	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**
Control	-	261.20±3.10	253.90±3.08	253.18±4.10	256.15±2.65	254.40±2.90	257.50±1.30	255.80±3.60	259.45±2.98
F.racemosa	100mg/kg	301.16±2.50	294.70±3.48	289.19±4.56*	273.25±2.27**	244.53±1.23***	195.94±1.95***	212.60±2.52***	207.82±2.10***
F.racemosa	200mg/kg	271.85±2.65	262.38±2.65*	251.67±2.99***	244.44±3.50***	220.34±1.65***	168.88±1.54***	177.03±0.96***	243.70±2.50***
F.racemosa	300mg/kg	291.56±1.60	278.29±2.50***	267.74±3.47***	252.92±3.05***	228.15±2.41***	152.25±2.60***	175.84±1.95***	201.22±3.02***
Glibenclamide	10mg/kg	288.20±2.49	275.38±2.13**	259.65±1.85***	248.07±2.98***	219.63±2.98***	139.20±1.96***	168.05±1.86***	190.75±1.92***

All blood glucose values were expressed as Mean ± S.E.M of five animals.

All blood glucose values were compared with corresponding values of control groups by using one way ANOVA dunett's test.

Statistical significant difference were expressed as *p<0.05, **p<0.01, ***p<0.001

2.5 Acute oral toxicity

Healthy Swiss albino mice of either sex, starved divided into 5 groups and orally fed the MEMI in increasing dose level of 250, 500, 1000, 1500, 2000 mg/kg body weight. Mice were observed for 24 hours for any lethality [18].

2.6 Effect on normal rats

Group I, II, III were given the ethanolic extract of *Ficus racemosa* leaves (suspended in 5% gum acacia) orally following a standard procedure19, at doses of 100, 200, 300 mg/kg body weight respectively. Animals in group IV received Glibenclamide at a dose of 10mg/kg body weight and served as standard. Group V served as a normal control and received appropriate volumes of vehicle orally.

2.7 Induction of diabetes

Group VI-X were rendered diabetic by injecting a freshly prepared aqueous solution of alloxan monohydrate (110 mg/kg, i.p.) after a base line blood glucose estimation was done [20]. After two weeks when the condition of *diabetes* was stabilized, animals with blood glucose levels above 250 mg/dl were selected for the study.

2.8 Effect on diabetic rats

Group VI-VIII were treated with ethanolic extract of *Ficus racemosa* leaves (suspended in 5% acacia) in the form of mucilage orally by gavage at doses of 100, 200, 300 mg/kg body weight, respectively. Group X served as a diabetic control and received appropriate volume of the vehicle orally while group IX received Glibenclamide at a dose of 10mg/kg body weight and served as a standard.

2.9 Collection of blood and determination of blood glucose

Blood samples were collected from the retro-orbital plexus under light ether anesthesia before and at 0.5, 1, 2, 4, 6, 8 and 12 h after drug administration. The samples were analyzed for blood glucose content by using glucose-oxidase method [21] with optical density measured by visible spectrophotometer at 520 nm.

2.10 Statistical analysis

All values were expressed as means ± standard error of means. Statistical comparisons were made by using one way ANOVA and Dunnett's *t*-test [22] by using graph pad prism 4.0 software. P values $p<0.05$ were considered as significant.

3. Results

Acute toxicity study revealed the non toxic nature of extract of *F.racemosa* leaves upto 2000 mg/kg. There was no lethality or any toxic reactions found at any of the doses selected until the end of the study period.

Preliminary phytochemical screening reveled the presence of alkaloids, glycosides flavonoids, phenolic compounda and tannins.

3.1 Effect of leaves extract on blood glucose levels in normal rats

The mean blood glucose concentration of control and drug-treated animals (after oral administration of different doses of *F.racemosa* leaves extract) at various time intervals are shown in Table I a dose dependent hypoglycemia was observed in animals treated with *F.racemosa* leaves extract. A significant reduction ($p<0.001$) in blood glucose of 20.82%, 24.28% and 26.33% was observed at the 6 h with doses of 100,200 and 300 mg/kg body weight respectively. the present study ethanolic extract of the *F.racemosa* leaves suppressed blood glucose levels in normal and alloxan induced diabetic rats, when compared to control animals. The hypoglycemic potential of the extract was comparable with that of the Glibenclamide in normal and diabetic rats. On the other hand, Glibenclamide caused significantly ($p<0.001$) more hypoglycemia in comparison with the plant extract at 300 mg/kg body weight ($p<0.001$).

There were also significant reductions starting 1 h following treatment. The maximum reduction was observed 6 h after treatment.

3.2 Effect of leaves extract on blood glucose levels in diabetic rats

The mean blood glucose concentration of control, *F.racemosa* treated (100, 200 and 300 mg/kg, p.o.) and Glibenclamide were treated (10 mg/kg, p.o.) rats are shown in Table II dose dependent Antihyperglycemic activity was also observed *F.racemosa* in alloxan induced diabetic rats. The percentage reduction of blood glucose was higher in the diabetic state compared to the normal state by the three doses of *F.racemosa*. a significant reduction ($p<001$) in blood glucose of 35.06%, 38.03% and 47.92% was observed at 6 h with the doses of 100, 200 and 300 mg/kg body weight, respectively. There were also significant reductions starting 2 h following treatment. The maximum reduction was observed 6 h after treatment. Glibenclamide produced a significant reduction ($p<0.001$) in blood glucose compared to diabetic control at the 6 h (53.56%).

4. Discussion

Diabetes mellitus is possibly the world's largest growing metabolic disease, and as the knowledge on the heterogeneity of this disorder is advanced, the need for more appropriate therapy increases [23]. Traditional plant medicines are used throughout the world for a range of diabetic presentations. The study of such medicines might offer a natural key to unlock a diabetologist's pharmacy for the future. The treatment goal for patients with type 2 *diabetes* mellitus is generally to achieve normal glycemic control in patient with type 2 *diabetes* mellitus. Type-II *diabetes* is characterized by reduced circulating concentration of insulin; poor insulin sensitivity or insulin resistance and poor glucose tolerance resulting in high blood glucose level. *Diabetes* mellitus of long duration is associated with several complications such as atherosclerosis, myocardial infarction, and neuropathy etc. These complications have long been assumed to be related to chronically elevated glucose levels and subsequent oxidative stress. There is a need for drugs, which lower the elevated blood glucose levels and also reduce oxidative stress to prevent long term complications [24].

Alloxan causes a massive reduction in insulin release by the destruction of β cells of the islets of Langerhans and induces hyperglycemia. Alloxan exerts its diabetogenic action when it is administered parenterally, intravenously, intraperitoneally or subcutaneously [25].

Flavonoids, steroids/triterpenoids, alkaloids and phenolics are known to be bioactive antidiabetic principles [26]. Flavonoids are known to regenerate the damaged beta cells in alloxan diabetic rats. *F.racemosa* reported to be possessed alkaloid, flavonoids, phenolic compounds and tannins which confirmed by phytochemical analysis. On the basis of above evidence it seems possible that the presence of alkaloid, flavonoids, phenolic compounds and tannins may be responsible for the observed antidiabetic activity.

5. Conclusion

Our results have showed that leaves of *F.racemosa* possess blood glucose lowering effect in normoglycemic and in alloxan induced hyperglycemic rats. Thus the folk use of this plant may be validated by this study.

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