The Journal of Phytopharmacology 2014; 3(6): 431-435
Online at: www.phytopharmajournal.com

Research Article

ISSN 2230-480X
JPHYTO 2014; 3(6): 431-435
November- December

Protective effect of *Ficus infectoria* plant extract against fructose induced hyperlipidemia and hyperglycemia in rats

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ABSTRACT

The main aim of this study is to explore the antihyperlipidemic and hypoglycemic potential of the methanolic extract of *Ficus infectoria* in Wistar rats. Hyperlipidemia and hypoglycemia in rats were induced by fructose solution (10% w/v, p.o., ad libitum) for 3rd and 8th weeks respectively. These activities were measured by estimating the triglyceride, total cholesterol, LDL, VLDL, HDL and serum glucose levels. *F. infectoria* at 200mg/kg and 400mg/kg showed significant effect. Fructose feeding increased serum biochemical parameters like triglyceride, total cholesterol, LDL, VLDL and serum glucose levels while decreases the HDL level. In fructose fed rats, *F. infectoria* at 200 mg/kg and 400 mg/kg significantly prevented the increase in serum biochemical parameters while decrease in HDL level. The present study indicates that methanolic extract of *F. infectoria* has Antihyperlipidemic and hypoglycemic. In future it may be useful in the management of insulin resistant.

Keywords: *Ficus infectoria*, Antihyperlipidemic, Hypoglycemic, Insulin Resistant, Fructose.

INTRODUCTION

It is believed that approximately 80% of the world population is almost entirely dependent on traditional medicine.[1] Medicare which involves direct use of plants for preventing and healing diseases and infections.[2] Such plants serve the primary healthcare needs of up to 80 % of people in developing countries where there is increasing awareness of and demand for medicinal plants for healthcare and dietary supplements that often help to save lives.[3] *Ficus infectoria* is one of such medicinal plant which is used in different illness conditions.

Ficus infectoria (*F. infectoria*) belongs to the Family Moraceae. Its common name is White Fig. It is locally known as Pilkhan. It is a large spreading tree, with occasional aerial root, found throughout the plains and lower hills. They are also found in Bangladesh, Nepal, Pakistan, Sri Lanka, Southwest China & Indochina. [4, 5]The stem bark contains Methyl ricinolate, Caffeic acid, Bergenin, β-sitosterol, lanosterol. Also contains fructose, sucrose, bergapten, bergaptol and flavonoids.[6] Decoction's of bark is used for washing ulcers, as a gargle in salivation; also used for menstrual disorders and leucorrhoea.[4] The bergapten and bergaptol isolated from the extract had shown antibacterial and antifungal activities.[7] Methanolic extract of *Ficus infectoria* possessed hyperglycemic properties in diabetic conditions.[8]

Hyperlipidemia is a secondary metabolic dysregulation associated with diabetes. Besides the cause effect relationship with diabetes, elevated serum level of triglycerides, cholesterol and LDL are major risk factors for the premature development of cardiovascular disease like arthrosclerosis, hypertension, coronary heart disease etc.[9] Increased plasma lipid levels mainly total cholesterol, triglycerides and LDL along with decrease in HDL are known to cause hyperlipidemia which is the reason for initiation and progression of atherosclerosis impasse.[10] Antihyperlipidemic agents having various pharmacological actions are being tested clinically.[11]

The public health burden of type 2 diabetes mellitus (T2DM) has been dramatically increased worldwide. It has been shown that the risk for developing clinical diabetes is substantially increased in the state of impaired fasting glycemia or impaired glucose tolerance. Fasting hyperglycemia is caused by unrestrained basal hepatic glucose output, primarily a consequence of hepatic resistance to insulin action. Insulin resistance not only plays an important role in T2DM but it also is an extremely common feature of a number of important human diseases including atherosclerosis, hypertension, and dyslipidemia.[12]

So, the present study was conducted to evaluate antihyperlipidemic and hypoglycemic activities of *F. infectoria* plant extract in fructose induced hyperlipidemia and hypoglycemia.

MATERIALS AND METHODS

Collection of Plant material-

The fresh leaves and bark of *Ficus infectoria* plant were collected in the month of October from Sultanpur district, Uttar Pradesh, India. The plant material was authenticated by Dr. Tariq Husain (Head & Scientist, Biodiversity & Angiosperm Taxonomy), National Botanical Research Institute, (NBRI) Lucknow, India (Accession No. 097837). A specimen sample of the same was preserved in the herbarium section of the College of Pharmacy, Teerthanker Mahaveer University, Moradabad for further reference.

Preparation of plant extracts-

The leaves and bark of *Ficus infectoria* were cleaned and shade dried in open air for 8-10 days then pulverized to dry power using electric grinder. About 80 gm of the dried leaf and bark powder (mixture) was extracted with hot solvents of methanol for 24 hours with each solvent, using the Soxhlet apparatus at a temperature of 30 to 35˚C. The extract was concentrated by vacuum rotary evaporator and stored in a refrigerator at 4˚C.

Chemicals and Instruments-

Fenofibrate (Finolip 145), 20 mg/kg (Cipla Pvt Ltd.); Fructose, 10% w/v solution (CDH Laboratory reagent); Carboxy Methyl Cellulose, CMC (Loba chemie); Methanol extract of *Ficus infectoria*; Hydrogen peroxide, Bio analyzer (Star 21 Plus); Vacuum Rotary Evaporator (Biogen certified); Glucometer (Bhat Bio-Tech India P Ltd.); Enzymatic kit (ARBA diagnostics kit).

Maintenance of animals and approval of protocol-

30 Wistar albino rats of either sex weighing between 150 and 200 g were used in this study. These rats were procured from the Central Animal House Facility, Teerthanker Mahaveer University, Moradabad. They were housed in well ventilated stainless-steel cages at room temperature (24 ± 2) ºC in hygienic condition under natural light and dark schedule and were fed on standard laboratory diet. Food and water were given ad libitium. Permission for the use of animal and animal protocol was obtained from the Institutional Animal Ethical Committee (IAEC) of Committee for the Purpose of Control and Supervision of Experiments on Animals (Reg. No. 1205/c/08/CPCSEA, Dated:-21/4/2008).

Fructose induced hyperlipidemia:

Fructose induced hyperlipidemia of *Ficus infectoria* leaf and bark extract was determined by method as reported by Omprakash N *et.al*. (2010).[13] Wistar rats weighing between 125-200 gm were divided into five groups of six animals each. The animals of the control group had free access to tap water while other groups were fed with food pellet and water ad libitum. 10% fructose was used as inducing agent for hyperlipidemia.

Group I- served as control group received vehicle (saline) daily for 20 days.

Group II- served as toxic control received 10% fructose solution for 20 days

Group III- served as standard received Fenofibrate at a dose of 20 mg/kg along with 10% fructose solution for 20 days.

Group IV- served as test-I received leaf and bark methanolic extract at a dose of 200 mg/kg along with 10% fructose solution for 20 days.

Group V- served as test-II received leaf and bark methanolic extract at a dose of 400 mg/kg along with 10% fructose solution for 20 days.

All the animals were fasted for half an hour prior to drug administrations. On day 21, these animals were anaesthetized with "diethyl ether". The blood was collected by retro orbital puncture and the serum was separated for estimation of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and very low density lipoprotein (VLDL) levels.

For estimation of triglycerides, cholesterol and HDL, kits (ARBA diagnostics kit, India) were used. All the estimations were carried out as per the instruction provided by the kit manufacturers. VLDL and LDL were calculated as per Friedewalds equation (mg/dl).[14]

VLDL = TG/5.0

LDL = TC - HDL - VLDL

Fructose induced Hyperglycemia:

The above respective treatment which was used for induction of hyperlipidemia continued till the 8th weeks except group III (Standard). The group III was discontinued after the 3rd weeks. Within the 8th weeks 10 % w/v fructose diet cause Insulin resistant[12] in rats and due to this the level of glucose increases. Estimation of blood glucose level of the animals were taken at 0, 3, 5 and 8th week. Collection of blood performed through the retro orbital puncture. Estimation of blood glucose level performed with the help of Glucometer.

Statistical analysis-

The statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Bonferroni Multiple Comparisons Test by using Graph Pad InStat (File version 3.0.10.0). The values were expressed as mean ± Standard Error Mean (SEM) for six rats in each group and $P<0.05$ were considered significant.

RESULTS

Antihyperlipidemic Activity-

The antihyperlipidemic activity of *Ficus infectoria* leaf and bark extract (methanolic) was determined by estimating the suppression of elevated lipid profile (triglyceride, total cholesterol, LDL & VLDL) except HDL (elevation of suppressed level) in fructose induced hyperlipidemic Wistar rats.

Administration of 10 % fructose solution resulted in increase in serum levels of cholesterol, triglycerides, VLDL, and LDL. A significant reversal in serum levels of cholesterol, triglycerides, VLDL, and LDL levels was noticed in the animals treated with *F. infectoria* leaf and bark extracts when compared with the control group. (Table: 1) (Figure: 1)

Hypoglycemic activity-

Fructose-induced insulin resistance model in rats:

Fructose feeding significantly increased serum glucose level when compared to normal rats. (Table: 2) (Figure: 2) Giving *F. infectoria* (200 mg/kg and 400mg/kg) along with fructose feeding (10%) for 8th weeks significantly ($P <0.001$) reduced the serum glucose values when compared to fructose alone fed group. No significant change in plasma glucose level was observed in normal rats. (Table: 2)

A significant dose dependently decrease in serum glucose level was observed in fructose fed group from level 176.64 ± 1.71 to the level 165.35± 2.31mg/dl and 159.93 ± 1.42mg/dl after the treatment at a dose of 200mg/kg and 400mg/kg body weight respectively for 8th weeks. No significant change in plasma glucose level was observed in normal rats at a dose of 200mg/kg and 400mg/kg body weight (Table: 2).

Table 1: Effect of the methanolic extract (leaf and bark mixture) of *F. infectoria* on different biological parameters.

Group	Dose	Triglycerides mg/dl	Total Cholesterol mg/dl	VLDL mg/dl	HDL mg/dl	LDL mg/dl
Normal Control	-	96.69 ± 6.25	104.31 ± 4.17	19.23 ± 1.03	53.40 ± 4.26	31.83 ± 2.13
Toxic Control (Fructose)	10% Fructose	200.19 ± 6.69	215.72 ± 7.67	40.03 ± 1.38	27.61 ± 1.49	148.07 ± 7.91
Standard (Fenofibrate + Fructose)	20 mg/kg	124.49 ± 7.61***	123.50 ± 6.45 ***	24.89 ± 1.52***	43.34 ± 2.18***	55.25 ± 8.78 ***
Test I (Extract + Fructose)	200 mg/kg	181.41 ± 8.57**	183.99 ± 9.67 ***	36.28 ± 1.71**	32.83 ± 1.65*	114.91 ± 9.74 ***
Test II (Extract + Fructose)	400 mg/kg	152.90 ± 7.36***	168.27 ± 5.25***	30.57 ± 1.47***	38.35 ± 1.20***	99.34 ± 4.93 ***

Results expressed as mean± standard error mean (SEM) and ***P<0.001 as compared to toxic control, **P<0.01 as compared to Toxic control, *P<0.05 compared to toxic control.

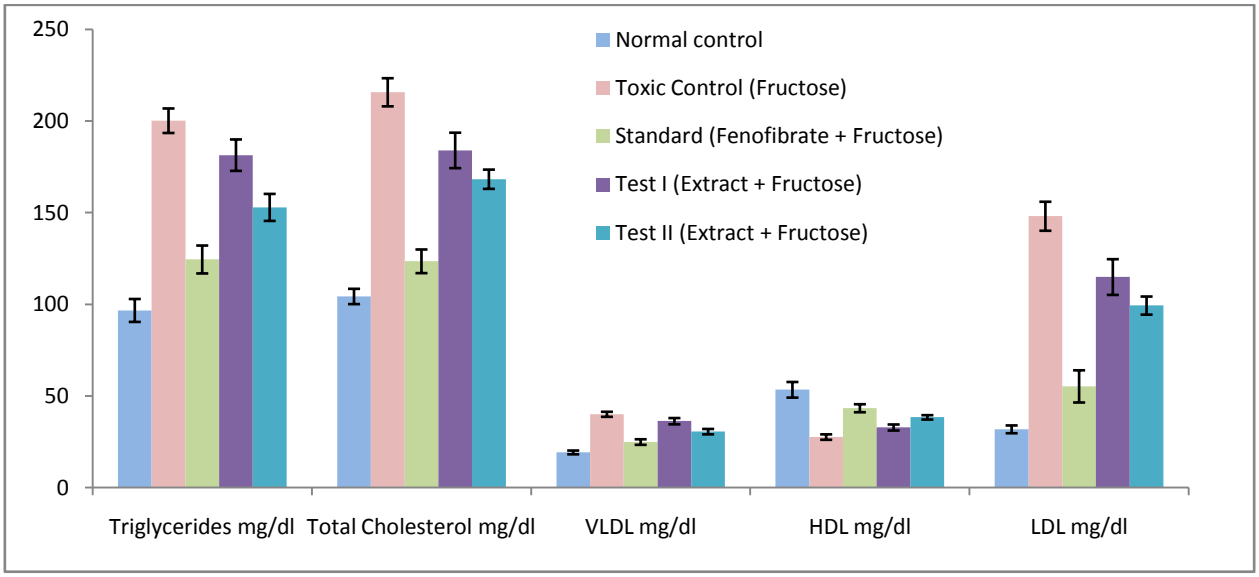

Figure 1: Graph showing variation in different parameter levels of Triglycerides, Total Cholesterol, VLDL, HDL and LDL against Fructose (10% Solution) Toxic group.

Table 2: Effect of the methanolic extract (leaf and bark mixture) of *F. infectoria* on blood glucose level of different groups of animals.

Group	Dose	Blood Glucose Level (mg/dl)			
		0 Week	3rd Weeks	5th Weeks	8th Weeks
Normal Control	-	155.12 ± 0.57	155.59 ± 0.73	154.92 ± 0.52	156.20 ± 0.82
Toxic Control (Fructose)	10% Fructose	154.16 ± 1.97	166.64 ± 1.21	172.96 ± 1.69	176.64 ± 1.71
Test I (Extract + Fructose)	200 mg/kg	158.47**ns** ± 1.14	163.02* ± 0.69	165.85** ± 1.69	165.35*** ± 2.31
Test II (Extract + Fructose)	400 mg/kg	156.84**ns** ± 1.42	161.61** ± 0.56	163.10*** ± 0.73	159.93*** ± 1.42

Results expressed as mean± standard error mean (SEM) and ***P<0.001 as compared to toxic control, **P<0.01 as compared to Toxic control, *P<0.05 compared to toxic control. ns stand for Not Significant.

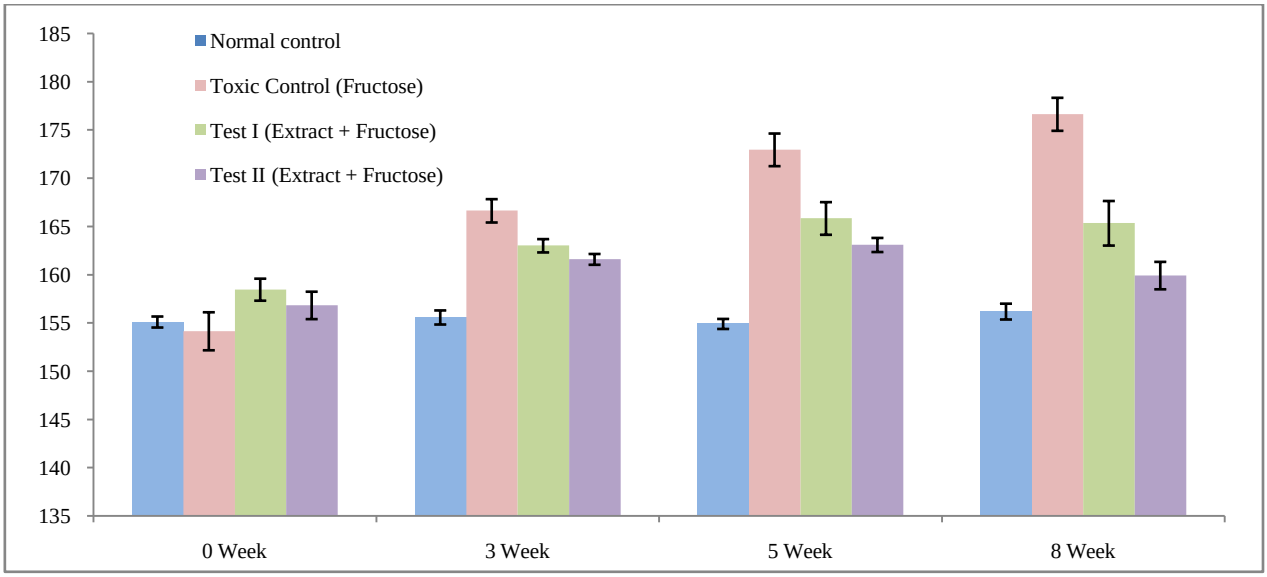

Figure 2: Graph showing variation in different weeks of blood glucose level (mg/dl) against Toxic Control (10% w/v Fructose solution) group.

DISCUSSION

The results obtained in this study showed that methanol extract of *F. infectoria* possess antihyperlipidemic and hypoglycemic activity.

Although fructose in the diet alters the activity of several enzymes and regulates hepatic carbohydrate metabolism, leading to hepatic insulin resistance[15] and hypertriglyceridaemia[16] the mechanisms by which an excess of fructose produces these effects are unknown. The use of 10 % fructose in drinking water for a period of 1 week or longer is equivalent to a diet containing 48-57 % by calories and has been found to be the most suitable one for the production of insulin resistance in rats.[17]

Insulin resistance in humans has been shown to be present in conditions like noninsulin-dependent diabetes mellitus (NIDDM), obesity and dyslipidemia. Thus interventions to decrease insulin resistance may postpone the development of NIDDM and its complications. Treatment with natural herbs is likely to be fraught with lesser side effects compared to the presently used synthetic oral anti diabetic agents.[18] The rats fed with high fructose diet induced a nonobese model of hyperlipidemia, insulin resistance, hyperinsulinemia and mild hypertension, which are features associated with obesity-related hypertension. In our study, administration of fructose for 20 days significantly increased the glucose, insulin and triglyceride levels similar to an earlier study.[12] Administering *F. infectoria* (200 mg/kg and 400mg/kg) prevented the development of hyperlipidemia and hyperglycemia.

The *F. infectoria* might have improved insulin resistance through enhanced insulin sensitivity in peripheral tissues, as was evident from the decreased glucose and insulin and increased liver and skeletal muscle glycogen stores. The drugs ameliorating hyperinsulinemia are likely to have greater therapeutic potential as they may also exert beneficial effects on the clinical course of NIDDM, hypertension and coronary artery disease conditions.

CONCLUSSION

Result of this study shows that oral administration of *F. infectoria* lowers serum glucose, triglyceride, total cholesterol, LDL and VLDL while increase HDL concentrations in fructose-fed rats. If these results are extrapolated to humans then *F. infectoria* might prove useful in the treatment and/or prevention of insulin resistance in non diabetic states such as obesity and impaired glucose tolerance.

Acknowledgments

The authors are thankful for Director College of Pharmacy and authority of Teerthanker Mahaveer University, Moradabad, India for providing the facility to carry out the research works.

Conflict of interest

There is no conflict of interest.

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