World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

HYPOGLYCEMIC AND HYPOLIPIDEMIC ACTIVITIES OF *FICUS HISPIDA* FRUITS AND BARK IN ALLOXAN INDUCED DIABETIC RATS

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Article Received on 03/12/2017 **Article Revised on 24/12/2017** **Article Accepted on 14/01/2018**

ABSTRACT

Now a day's diabetes mellitus is one of the most common health problems. Retinopathy, nephropathy, angina pectoris, heart attack, transient ischemic attacks, strokes and peripheral arterial disease are the common complication of diabetes. Traditionally *Ficus hispida* Linn. (*F. hispida*) is used in herbal medicine for the treatment of diabetes for many years, but there is no sufficient data for its antidiabetic property. This study was undertaken to evaluate the antidiabetic and antihyperlipidemic activities of ethanol extracts of *F. hispida* fruits and bark in alloxan-induced diabetic rats. The results showed that *F. hispida* fruits and bark decreased blood glucose level significantly ($P<0.001$ to $P<0.01$) and also regulated parameters of lipid profile (TG, TC, LDL, VLDL, HDL) significantly ($P<0.001$ to $P<0.01$) in experimental model ofdiabetes mellitus. The levels of serum SGPT, SGOT and CRP were also adjusted to the normal levels notably ($P<0.001$ to $P<0.01$) by the intraperitoneal administration of ethanol extract of *F. hispida* bark (EB) and ethanol extract of *F. hispida* fruits (EF).Further studies are required to be done to isolate the active compounds from the *F. hispida* fruits and bark, elucidate their structures and their mode of action.

KEYWORDS: Diabetes mellitus, antidiabetic activity**,** ethanol extract, *Ficus hispida*, lipid profile.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease that arises when the pancreas fails to make sufficient amount of insulin, or when the body cannot use properly of the insulin it produces. Common complications of diabetes are retinopathy, angiopathy, neuropathy, etc.[1,2] Diabetes mellitus is a major global health problem, affecting 415 million adult people, accounting for 5 million deaths in 2015; 1 people die every six seconds from diabetes and 46% people with diabetes remain undiagnosed. The global annual cost of diabetes is more than USD 650 billion and by 2040 the number of affected people is expected to increase to 642 million globally.[3] In Bangladesh, a meta-analysis showed that the prevalence of diabetes among adults had increased substantially, from 4% in 1995 to 2000 and 5% in 2001 to 2005 to 9% in 2006 to2010 and the prevalence will be 13% by 2030.[4] It has been also reported that diabetes tends to increase low-density lipoprotein cholesterol and decrease high-density lipoprotein cholesterol levels in blood that leads to coronary occlusions and blocks.

Currently used synthetic drugs in the treatment of diabetes mellitus have got beneficial as well as adverse side effects.[5,6] Therefore it is required to find out new drugs for the treatment of diabetes mellitus with maximum efficiency and least side effects. Many plants have been found with antidiabetic activity experimentally.[7]

F. hispida belongs to the botanical family Moraceae is a small but well distributed species of tropical fig tree. It occurs in many parts of Asia and as far south-east as Australia.[8] Almost all parts of this plant are used in traditional medicine for the treatment of ulcers, psoriasis, anemia, piles, jaundice, vitiligo, hemorrhage, diabetes, convulsion, hepatitis, dysentery, biliousness and purgative.[9] There is no sufficient scientific data on its antidiabetic and antihyperlipidemic properties. Therefore this study was under taken to evaluate the antidiabetic and antihyperlipidemic activities of *F. hispida* fruits and bark.

MATERIALS AND METHODS

Collection of plant material and authentication

Mature *F. hispida* fruits and bark were collected from local area of Rajshahi (north-western part of Bangladesh)

in January, 2017 and authenticated by the Department of Botany, University of Rajshahi, Bangladesh.

Preparation of extract

The fruits and bark were first washed with water to remove adhering dirt. Then the fruits and bark were chopped into small pieces and shed dried. After complete drying, the entire portions were ground into coarse powder by a grinding machine and stored in an airtight container for further use. Then 70 g of the powdered material was taken in separate clean, round-bottomed glass bottle and soaked in 350 ml of solvent. The container with its content was sealed by cotton plug and aluminum foil and kept for a period of 15 days accompanying occasional shaking and stirring. The resulting extracts were filtered through Whatman No. 1 filter paper. Afterwards, the solvents were evaporated under reduced pressure at 40˚C using rotary evaporator. Finally, the residues were kept in small sterile bottles under refrigerated conditions until used.

Chemicals

Alloxan monohydrate was purchased from Sigma chemical Co. All others chemical were used in analytical grade and were acquired from commercial sources.

Animal care

Male albino rats (wistar strain) weighing 100-120gm were collected from International Cholera and Dysentery Disease Research, Bangladesh (ICDDR, B) for the study. They were individually housed in polypropylene cages in well-ventilated rooms (temperature 25±2^{o}C; humidity 55±5% with 12h light/dark cycle), under hygienic conditions. Rats were allowed free access to standard dry pellet diet and water.

Induction of diabetes

Diabetes was induced in overnight fasted rats by a single intra-peritoneal injection of alloxan (90mg/kg body weight) in a 0.1M sodium citrate buffer (pH 4.5). The age matched control rats received an equivalent amount of citrate buffer. Food and water intake were closely monitored daily after Alloxan administration. The development of hyperglycemia in rats was confirmed by fasting (16h) blood glucose measurement in the tail vein blood, 48h after alloxan administration, with a portable glucometer. The animals with fasting blood glucose level ≥11.0mmol/l with other symptoms of diabetes mellitus such as polyphagia, polydipsia, polyuria, and weight loss were considered diabetic and included in this study.

Experimental groups

The animals were randomly divided into seven groups and each group consisted of six animals (n=6). The animals were treated for 3 weeks as follows:

- **Group-1 (NC):** Untreated normal control rats.
- **Group-2 (DC):** Untreated diabetic control rats.
- **Group-3 (EB 100):** The diabetic rats treated with EB at a dose of 100 mg/kg body weight (BW) for 21 days.
- **Group-4 (EB 200):** The diabetic rats treated with EB at a dose of 200 mg/kg BW for 21 days.
- **Group-5 (EF 100):** The diabetic rats treated with EF at a dose of 100mg/kg BW for 21 days.
- **Group-6 (EF 200):** The diabetic rats treated with EF at a dose of 200 mg/kg BW for 21 days.
- **Group-7 (PC):** Diabetic rats were treated by Glibenclamide (positive control) at a dose of 5 mg/kg BW for 21 days.[10,11]

Collection of blood

Collection of blood samples from the tail veins ofeach mouse was carried out before the start of the treatment and on day 1, 5, 10, 15 and 21during the treatment. At the end of experiment period, rats were sacrificed after overnight fasting by anesthetizing with diethyl ether and blood was collected from the heart and storedat -20°Cimmediately till further analysis.

Measurement of blood parameters

Blood glucose level was measured by glucose oxidase-peroxidase method.[12] Parameters of serum lipid profile such as triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were measured using commercially available kits. Serum SGPT, SGOT and CRP levels were also estimated using commercially available kits. Hitachi 7180 automatic analyzer (Hitachi, Tokyo, Japan) was used to estimate these biochemical parameters.

Statistical analysis

All values were expressed as mean ± SD (Standard Deviation). Statistical analysis was performed with one-way analysis of variance (ANOVA) followed by Dunnett's t test using SPSS software of 16 version. $P<0.05$ were considered to be statistically significant.

RESULTS

Effects of EB and EF on blood glucose level

Administration of alloxan in rats significantly ($P<0.001$) increased the blood glucose levels compared to the normal control group. Oral administration of EB and EF at doses 100 and 200 mg/kg BW decreased blood glucose level in diabetic rats significantly ($P<0.001$ to $P<0.01$) compared to the diabetic control group (Table 1).These level of reduction was as near as glibenclamide administeredgroup ($P<0.001$). At the end of the treatment, EB at both doses (100 and 200mg/kg BW) lowered the glucose level by 43.43% and 54.54%, EF at both doses (100 and 200 mg/kg BW) decreased blood glucose level by 39.86% and 45.41% respectively, while glibenclamide (5mg/kg BW) reduced the glucose level by 14.56%-64.15% than the diabetic control group.

Effects of EB and EF on lipid profile

Table 2 represented serum levels of total cholesterol (TG), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density

lipoprotein (VLDL) in the each group of experimental rats. TG, TC, LDL and VLDL levels were increased in alloxan induced diabetic ratswhereas HDL level was decreased significantly (P<0.001) compared to that of normal control group. Oral administration of EB and EF at both doses (100 and 200 mg/kg BW) regulated those parameters of lipid profile in diabetic rats reversely towards the normal level significantly (P<0.001 to P<0.01) compared to the diabetic control group.

Table 1: Effects of EB and EF on blood glucose level in diabetic rats after 21 days of treatment.

Groups of animals		Serum glucose concentration (mmol/L)				
		Day 1	Day 5	Day 10	Day 15	Day 21
NC		5.66±0.21	5.52±0.42	5.68±0.26	5.76±0.33	5.52±0.42
DC		17.95±0.89[a]	18.89±0.56[a]	19.73±0.88[a]	21.82±0.76[a]	22.68±0.82[a]
Treat-ment	EB 100	17.82±2.52	17.46±1.35[b]	15.49±0.91[b]	14.24±0.76[b]	12.83±0.94[c]
	EB 200	18.35±1.35	16.81±1.75[b]	14.95±1.42[b]	12.76±1.62[c]	10.31±1.07[c]
	EF 100	17.68±0.96	16.28±1.21[b]	15.07±0.89[b]	14.79±0.92[b]	13.64±1.13[c]
	EF 200	17.85±1.34	16.73±0.91[b]	14.67±0.49[b]	13.42±0.53[c]	12.38±0.37[c]
PC		18.52±0.98	16.94±1.42[b]	12.76±0.92[c]	9.14±0.73[c]	8.13±1.18[c]

All values are expressed as mean±standard deviation (n=6). [a]P<0.001compared with general control group; [b]P<0.01 and [c]P<0.001 compared with diabetic control group.

Table 2: Effects of EB and EF on biochemical parameters of lipid profile in diabetic rats after 21 days of treatment.

Groups of animals	Parameters				
	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
NC	78.95±1.01	89.56±3.18	48.56±2.97	12.47±1.17	17.91±0.24
DC	132.58±4.28[a]	146.21±3.40[a]	30.72±1.51[a]	72.62 ± 2.84[a]	29.24±1.28[a]
EB 100	115.02±1.40[b]	123.38±1.76[b]	40.45±1.16[b]	49.89± 2.90[b]	24.67±0.75[c]
EB 200	102.93±3.83[b]	110.90±3.62[b]	47.23±2.32[b]	33.52±1.32[b]	22.18±1.22[b]
EF 100	121.28±2.87[c]	130.85±4.59[b]	38.02±2.07[b]	57.09±1.32[b]	26.17±0.92[c]
EF 200	115.72±3.43[b]	120.33±4.92[b]	42.49±1.74[b]	49.17±4.27[b]	24.06±0.83[b]
PC	91.27±4.08[b]	96.12±3.42[b]	48.42±2.07[b]	23.63±2.52[b]	19.22±1.28[b]

Results are expressed as mean±standard deviation (n=6). [a]P<0.001 compared with normal control (NC) group, [b]P<0.001 and `` P<0.01 compared with diabetic control (DC) group.

Effects of EB and EF on serum SGPT, SGOT and CRP level

SGPT and SGOT levels were increased significantly (*P*<0.001) in diabetic rats compared to the normal rats and these were also compensated considerably (*P*<0.001 to *P*<0.01) by the oral administration of EB, EF and glibenclamide (Figure 1). EB reduced serum SGPT level at both doses (100 and 200 mg/kg BW) by 23.24% and 37.16%, SGOT level by 21.24% and 27.95% respectively whereas glibenclamide decreased serum SGPT and SGOT levels by 42.65% and 40.83% respectively. EF also lowered serum SGPT level at both doses (100 and 200 mg/kg BW) by 14.87% and 30% whereas SGOT level by 17.56% and 24.63%respectively. In diabetic condition, the level of C-reactive protein (a potent marker of hepatic and cardiovascular diseases) is also increased in diabetic condition. The oral administration of EB and EF reduced the C-reactive protein (CRP) level significantly (*P*<0.01 to*P*<0.05 and *P*<0.001), which are quite similar to glibenclamide treated diabetic rats (Figure 2). EB reduced CRP level in diabetic rats by 25.37% and 40.07% at doses 100 and 200 mg/kg BW respectively, where EF decreased CRP level in diabetic rats by 21.32% and 29.04% at doses 100 and 200 mg/kg BW considerably.

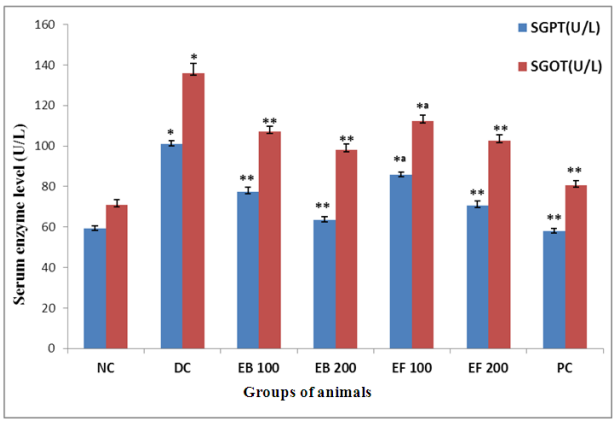

Figure 1: Effects of EB and EF on liver function marker enzymes in diabetic rats.

*Results are expressed as mean ± standard deviation (n=6). *P<0.001 compared with normal control (NC) group; **P<0.001 and *[a]P<0.01 compared with diabetic control group.*

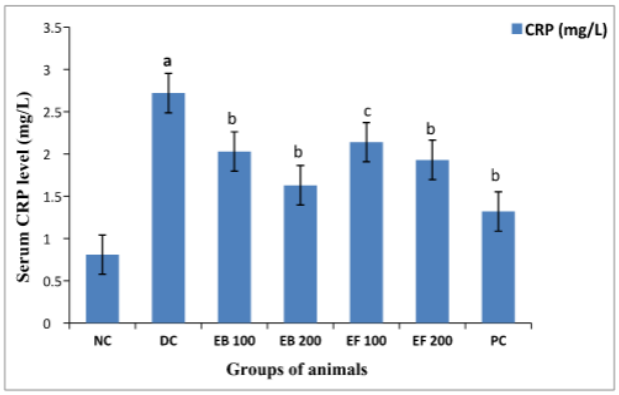

Figure 2: Effects of EB and EF on serum CRP level of diabetic rats after 21 days of treatment.

All values are expressed as mean±standard deviation (n=6). [a]P<0.001 compared with normal control group; [b]P<0.01and [c]P<0.05compared with diabetic control group.

DISCUSSION

In our present study, the alloxan induced diabetic rats represented 3 to 4 fold increase in blood glucose level compared to the normal rats. Alloxan destroys and decreases the population of pancreatic β-cell through the formation of oxygen species.[13] In diabetic condition lipid profile also changes. An increase level of total cholesterol, LDL, triglycerides, VLDL and decrease in HDL was foundin alloxan-induced diabetic rats compared to that of control rats which is similar to previous study.[14-16] Our current study clearly indicated that the oral administration of FB and FF have significant (P<0.001 to P<0.01) antidiabetic and antihyperlipidemic activities, which are quite similar to the antidiabetic and hypolipidemic activities of glibenclamide (P<0.001) in alloxan induced diabetic rats compare to the diabetic control rats. EB showed maximum antidiabetic activity was found at dose 200 mg/kg BW among four doses of EB and EF, where blood glucose level was decreased by 54.54% compared to the diabetic control group. Blood glucose level was also reduced notably by the other three doses of EB and EF.

In this current study, EB and EF represented significant(P<0.001 to P<0.01) hypolipidemic activity in diabetic rats. EB showed maximum hypolipidemic activity between EF and EB. Antihyperlipidemic activity of EB at dose 200 mg/kg BW was found almost similar to the antihyperlipidemic activity of glibenclamide in diabetic rats at dose 5 mg/kg BW. At this dose EB decreased serum TC level by 22.36%, TG level by 24.15%, LDL level by 53.84%, VLDL level by 24.16% and increased HDL level by 53.74%. These results are quite similar with the findings of some previous studies which alsoconfirmed the hypoglycemic andhypolipidemic activities of plant extract in diabetic animal model.[14-19]

In diabetic condition, SGOT and SGPT levels are also increased as an indication of the liver damage.[20,21] Oral administration of EB, EF and glibenclamide significantly decreased their levels in diabetic rats. In addition, CRP is a marker of systemic inflammation, which is emerging as an independent risk factor for cardiovascular disease.[22,23] The serum CRP level is elevated in diabetic patients which has been reported previously.[24] In our present study, EB and EF reduced serum CRP level significantly (P<0.001 to P<0.05) in diabetic rats.

CONCLUSION

From this study it can be concluded that the ethanol extract of *F. hispida* bark (EB) and fruits (EF) possess potent antidiabetic and hypolipidemic activities. Again between EB and EF, EB showed maximum antidiabetic and antihyperlipidemic activities in diabetic rats. Therefore, it may be used for the treatment of diabetes, cardiovascular diseases and complications associated with these diseases in future.As it is found everywhere of Bangladesh as well as all parts of Asia and some other regions, it may be cost effective for the people of these region living with those complications. In addition, further study is required to understand its mechanism of action and to identify and isolate compounds responsible for these activities.

ETHICAL APPROVAL

Approval and permission of using rat model for our present study were obtained from the Institute of Biological Sciences (IBSc), University of Rajshahi, Bangladesh (Approval No: 86/320/IAMEBBC/IBSC).

ACKNOWLEDGEMENT

Authors are grateful to the Department of Biochemistry and Molecular Biology, University of Rajshahi, Bangladesh for providing necessary materials.

CONFLICT OF INTEREST

Authors have declared that no competing interests exist.

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