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Hypoglycemic, Hypolipidemic and Antibacterial Activity of *Ficus racemosa* Fruit Extract

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Authors' contributions

This work was carried out in collaboration between all authors. Author NH designed the study. Authors NH, FS, MAJK, MHB, AI, NT, MDI, TA and KZR carried out the tests and managed the analyses of the study. Author MRUK managed the literature searches. Author MMH performed statistical analysis. Authors MAM and MA wrote the first draft of the manuscript. Authors MMR and MAI reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: *Ficus racemosa*, popularly known as the fig or cluster fig, is a traditional plant in the Moraceae family with various ethnomedical uses. However, the information of medicinal values of Bangladeshi grown *Ficus racemosa* fruit extracts using different solvent systems is still lacking in the literature. Therefore, the present study was carried out to enrich the information of the medicinal property of *Ficus racemosa* fruit extract in terms of hypoglycemic, hypolipidemic and antibacterial activity.

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Methods: Methanol, ethanol, chloroform, n-hexane and petroleum ether solvents were used to obtain five different types of mature *Ficus racemosa* fruit extract by Soxhlet extraction process. Antibacterial activity of each extract was determined by disc diffusion method whereas ethanol extract was tested to evaluate its hypoglycemic and hypolipidemic activity by using alloxan-induced diabetic mice model.
Results: At the end of 21 days of treatment, ethanol extract decreased the blood glucose level of diabetic mice by approximately 41% and 50% at doses 100 and 200 mg/kg body weight, respectively, whereas at the same doses total cholesterol levels were decreased by approximately 16% and 17%, LDL reduced by 28% and 29%, HDL increased by 41% and 67% compared to the diabetic control group. The levels of SGPT, SGOT and CRP were also significantly (P<0.05 to P<0.001) reduced by administration of same doses of ethanol extract. At a concentration of 600 µg/disc, strong antibacterial activity was displayed by methanol, ethanol and petroleum ether extract against most of the tested bacteria with the zone of inhibition of 13 to 17 mm.
Conclusion: The present study revealed strong anti-diabetic and antibacterial activity of the fig extract and therefore suggested that this fruit may play a potential role in the treatment of diabetes mellitus and various bacterial infections.

Keywords: Ficus racemosa; hypoglycemic activity; hypolipidemic activity; antibacterial activity.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder of carbohydrate, fat and protein metabolism characterized by high levels of blood sugar due to the impaired production of insulin or insulin action [1,2]. It has been reported that 382 million of the world population is affected with DM and is expected to increase up to 592 million by 2035 [3]. It is now well established that hyperlipidemia is an important characteristics of DM and considered as a major risk factor for the premature development of atherosclerosis [4,5]. The available drugs for the treatment of DM, insulin or oral hypoglycemic agents such as sulfonylureas, thiazolidinediones etc., have one or more adverse effects [6]. Hence, search for new drugs with minimum or no side effects remains a challenge.

A high incidence of resistant microorganisms has been reported all over the world. Despite the advancement in the production of a number of new antibiotics in the last three decades, microbial resistance to these drugs has increased [7,8]. Hence, actions must be taken to reduce the growing problem of resistance to drugs by microorganisms.

Plants are an exemplary source of drugs; in fact many of the currently available drugs were derived either directly or indirectly from them. Research on herbal medicines is encouraged to come up with alternative for treatment of diabetes since plant drugs and formulations are considered to be less toxic and free from side effects than synthetic ones [9]. According to world ethno-botanical information reports, almost 800 plants may possess anti-diabetic potential [10]. Many plants have also been used because of their antimicrobial activities, which are due to compounds synthesized in the secondary metabolism of the plant [7].

Ficus racemosa belonging to the Moraceae family is a traditional plant mentioned in all ancient scriptures of Ayurveda, Siddha, Unani and Homeopathy. All parts of *F. racemosa* plant (leaves, fruits, bark, latex and sap of the root) are medicinally important in the traditional system of medicine in India [11]. Apart from the usage in traditional medicine, scientific studies indicated that *F. racemosa* possess various biological effects such as hepatoprotective, chemopreventive, antidiabetic, anti-inflammatory, antipyretic, antitussive and antidiuretic activity [12]. Antimicrobial activities of *Ficus racemosa* fruit extracts against several bacterial and fungal strains have also been reported [13]. However, the information of medicinal values of Bangladeshi grown *Ficus racemosa* fruit extracts using different solvent systems is still lacking in the literature. Therefore, this study was conducted to enrich the information of the medicinal property of *Ficus racemosa.* The objectives of the present study were to investigate the hypoglycaemic, hypolipidemic and antibacterial properties of different solvent extracts of *Ficus Racemosa* fruit.

2. MATERIALS AND METHODS

2.1 Plant Material

The fruits of *Ficus Racemosa* were collected in December, 2015 from Rajshahi, north-western region of Bangladesh which lies on 24°22′26″

north latitude and 88°36′04″ east longitudes, and authenticated by Botany Department, Rajshahi University. The fruits were washed with tap water and chopped into small pieces, which were then dried under shade and grinded.

2.2 Preparation of Extract

The shade-dried fruits were coarsely powdered and extracted with five different solvents namely methanol, ethanol, chloroform, n-hexane and petroleum ether by a Soxhlet apparatus at 45°C. The solvents were completely removed by rotary evaporator and obtained respective gummy exudates. These crude extracts were used for further investigation.

2.3 Animal Care

Swiss albino mice of both sexes weighing about 30 to 35 g were collected from the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr'b) and then individually housed in polypropylene cages in well-ventilated rooms, under hygienic conditions. Feeding of animals was done ad libitum, along with drinking water and maintained at natural day night cycle. The approval and permission of using mice model in this study were obtained from the Institute of Biological Sciences, University of Rajshahi, Bangladesh.

2.4 Induction of Diabetes

Diabetes was induced in overnight fasted animals by a single intraperitoneal injection of 5% solution of alloxan monohydrate (80 mg/kg body weight) (Sigma Chemical Co., USA) in a 0.1 M sodium citrate buffer (pH 4.5). The age-matched control animals received an equivalent amount of citrate buffer. Food and water intake were closely monitored daily after alloxan administration. The development of hyperglycaemia in animals was confirmed by fasting (16 hours) blood glucose measurement in the tail vein blood, 48 hours after alloxan administration, with a portable glucometer (Accu-Chek, Roche, Germany). The animals with fasting blood glucose level ≥ 11.0 mmol/L with other symptoms of diabetes mellitus such as polyphagia, polydipsia, polyuria, and weight loss were considered diabetic and included in the study [14,15].

2.5 Experimental Animal Grouping and Treatment

The test animals were randomly divided into five groups and each group consisted of six animals. The treatment of animals began on the 14th day of diabetes induction and this was considered as 1st day of treatment. The animals were treated for 3 weeks as follows:

Group-1: Control mice feed with standard pellet diet and water.

Group-2: These animals served as untreated diabetic control.

Group-3: Diabetic mice treated with ethanol extract of *Ficus racemosa* (EEFR) at a dose of 100 mg/kg body weight for 21 days.

Group-4: Diabetic mice treated with ethanol extract of *Ficus racemosa* (EEFR) at a dose of 200 mg/kg body weight for 21 days.

Group-5: Diabetic mice treated with glibenclamide at a dose of 5 mg/kg body weight for 21 days.

2.6 Blood Collection

Collection of blood samples from the tail veins of each mouse was carried out to measure the glucose level on days 1, 5, 10, 15 and 21 in a fasting state during the treatment. At the end of experiment period (after 21 days of treatment), mice were sacrificed after overnight fasting by anesthetizing with diethyl ether and blood was collected from the heart and immediately stored at -20℃ till further analysis.

2.7 Measurement of Blood Parameters

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 analyser (Hitachi, Tokyo, Japan) was used to estimate these biochemical parameters.

2.8 Antibacterial Assay

The agar disc diffusion method [16] was used to test antibacterial activity against eight different strains of pathogenic bacteria of which four are gram positive i.e. *Staphylococcus aureus*, *Bacillus cereus, Bacillus subtilis* and *Streptococcus pyogenes*, and remaining are gram negative i.e. *Escherichia coli*,

Agrobacterium tumefaciens, *Shigella dysenteriae* and *Salmonella typhi*. Solutions of known concentration (mg/ml) of the test samples were made by dissolving measured amount of the samples in calculated volume of solvents. Dried and sterilized filter paper discs (6 mm diameter) were then impregnated with known amounts of the test substances using micropipette. Discs containing the test materials were placed on nutrient agar medium uniformly seeded with the pathogenic test microorganisms. Standard antibiotic discs (Azithromycin 15 µg/disc) and blank discs (impregnated with solvents) were used as a positive and negative control, respectively. These plates were then kept at 4℃ in a refrigerator for 24 hours to allow maximum diffusion. After that, the plates were then incubated at 37℃ for 24 hours to allow maximum growth of the organisms on the culture medium. The test materials having antibacterial activity inhibited the growth of the microorganisms and a clear, distinct zone of inhibition was visualized surrounding the medium, termed as zone of inhibition. The antibacterial activity of the test agent was determined by measuring the diameter of zone of inhibition expressed in millimetre (mm). The antibacterial activity of five different extracts of *Ficus racemosa* fruit was determined at a concentration of 200, 400 and 600 µg/ disc.

2.9 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.

3. RESULTS

3.1 Hypoglycemic Effect of EEFR

Administration of alloxan resulted in significant elevation in serum glucose. Diabetic mice were treated with the ethanol extract of *Ficus racemosa* (EEFR) at the doses of 100 and 200 mg/kg body weight. Table 1 showed that EEFR produced significant changes in the blood glucose level in alloxan-induced diabetic mice. Comparing the blood sugar level in diabetic control mice, EEFR administered subject showed significant ($P<0.01$ to $P<0.001$) reduction of blood glucose level in both concentration (100 and 200 mg/kg body weight). These level of reduction was as near as glibenclamide administered subject. In 5^{th} to 21^{st} days of treatment, EEFR at both doses (100 and 200 mg/kg body weight) lowered the glucose level by 7%-41% and 7%-50%, respectively compared to the diabetic control group, while normal mice did not exhibit any significant alterations in serum glucose during the experiment.

3.2 Hypolipidemic Effect of EEFR

As shown in Table 2, the administration of EEFR (100 and 200 mg/kg body wt.) and glibenclamide significantly decreased serum triglycerides, total cholesterol, LDL and VLDL when compared with control diabetic mice. Administration of EEFR at doses 100 and 200 mg/kg body weight decreased total cholesterol by approximately16% and 17%, lowered LDL level by 28% and 29%, increased HDL level by 41% and 67% in diabetic mice compared to the control diabetic mice, respectively.

3.3 Effect of EEFR on Serum SGPT, SGOT and CRP Level in Diabetic Mice

There was a significant increase of SGPT and SGOT level during diabetic state which was significantly ($P<0.001$) compensated by administration of ethanol extract of *Ficus racemosa* (EEFR). The reduction of SGPT by this extract at both doses (100 and 200 mg/kg BW) was approximately 21% and 27% whereas SGOT level lowered by 37% and 44% in diabetic mice, respectively compared with control diabetic mice.

The level of C-reactive protein (CRP), a potent marker of hepatic and cardiovascular diseases, is also increased in diabetic condition. The administration of EEFR and glibenclamide reduced the CRP level significantly ($P<0.05$ and $P<0.001$). Compared to the diabetic control mice EEFR administration at 100 and 200 mg/kg BW doses lowered the CRP level by about 29% and 55% in diabetic mice, respectively (Fig. 2).

3.4 Antibacterial Property of *Ficus racemosa* Extracts

Five types of extract at three different concentrations (200, 400 and 600 µg/disc) were tested for their antibacterial property. Standard antibiotic disc Azithromycin (15 µg/disc) was used for comparison. Most extracts displayed bactericidal activity against different species of

Gram-positive and Gram-negative bacteria. No inhibition was observed with the control (DMSO) which was used as solvent to solubilize the dry extracts. The result obtained from this study is presented in Table 3. Methanol, ethanol and petroleum ether extract displayed almost similar inhibitory activities with the zone of inhibition ranged from 8 to 17mm which higher than that of chloroform and n-hexane extract.

4. DISCUSSION

Methanol, ethanol, chloroform, n-hexane and petroleum ether extract of *Ficus racemosa* fruits obtained by Soxhlet extraction process were investigated in our present study for their antibacterial property, whereas ethanol extract was investigated for its anti-diabetic effect. In a previous study carried out by our group with the above extracts, ethanol extract exhibited the highest antioxidant activity than the other four extracts [17]. Plant extracts rich in antioxidant activity have been reported by a number of researchers to possess beneficial effect in the management of diabetes mellitus [18]. Therefore in the current study, we have assessed anti-diabetic property of ethanol extract of *Ficus racemosa* using alloxan-induced diabetic mice model.

Alloxan, a hydrophilic and unstable chemical compound, is selectively up taken by GLUT2 glucose transporter of beta cells of pancreas and causes destruction of the pancreatic beta cells which is responsible for the reduction in insulin secretion [19,20]. The observed significant increase in blood glucose level of diabetic mice could be due to the destruction of pancreatic β-cells by alloxan administration. In diabetic condition lipid profile also changes. An increase level of total cholesterol, LDL, triglycerides, VLDL and decrease in HDL cholesterol was observed in alloxan-induced diabetic mice compared to that of control animals. The data of the present study clearly indicated that the oral administration of ethanol extract of *Ficus racemosa* fruit at both doses (100 and 200 mg/kg body weight) produced significant hypoglycemic and hypolipidemic effect in alloxan-induced diabetic mice compared with diabetic control mice. The results were consistent with findings of some previous studies which also

Table 1. Effects of ethanol extract of *Ficus racemosa* on serum glucose level

Groups of animals	Day 1	Day 5	Day 10	Day 15	Day 21
	Serum glucose level (mmol/L)				
General control	6.13±0.38	6.84±0.26	5.87±0.45	6.38±0 .28	5.84±0.39
Diabetic Control	19.48±0.33[a]	20.65±0.4[a]	20.74±0.47[a]	21.68±0.57[a]	23.33±0.35[a]
Diabetic+EEFR (100 mg/kg BW)	19.62±0.28	19.08±0.43	17.64±0.43[b]	16.11±0.62[b]	13.61±0.71[c]
Diabetic+EEFR (200 mg/kg BW)	20.04±0.41	19.38±0.43	17.03±0.23[b]	15.78±0.34[b]	11.56±0.16[c]
Diabetic+ Glibenclamide	21.1±0.32	16.54±0.41[b]	14.38±0.35[b]	11.44±0.54[c]	8.03±0.21[c]

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

Table 2. Effects of ethanol extract of *Ficus racemosa* on lipid profile in diabetic mice after 21 days treatment

Groups	Parameters				
	Cholesterol (mmol/L)	Triglyceri-des(mmol/L)	LDL (mmol/L))	HDL (mmol/L))	VLDL (mmol/L)
General Control	4.89±0.17	3.35±0.08	3.12±0.15	1.08± 0.03	0.69±0.02
Diabetic control	6.89±0.12*	4.68±0.13*	5.77±0.13*	0.46±0.03*	0.92±0.02*
Diabetic+EEFR (100 mg/kg BW)	5.76±0.22**	3.86±0.25	4.12±0.35**	0.65±0.02**	0.76±0.10**
Diabetic+EEFR (200 mg/kg BW)	5.72±0.21**	3.91±0.22	4.11±0.12**	0.77±0.02**	0.78±0.11**
Diabetic +Glibenclamide	3.88±0.16**	2.35±0.02	2.67±0.11**	0.82±0.01	0.47±0.01**

*Results are expressed as mean±standard deviation (n=6). *P<0.001 compared with general control and **P<0.05 compared with diabetic control*

confirmed hypoglycemic and hypolipidemic activities of the *Ficus racemosa* extract in diabetic animal model [21-25]. Therefore, ethanol extract of *Ficus racemosa* may be considered as a promising source of new lead compound for drug discovery for the treatment of insulin dependent diabetes mellitus.

A high incidence of resistant bacteria in clinical microbiology have been documented all over the world and it is also suspected that new and multi-resistant bacterial strain can develop in future which will cause new infection resulting in high mortality. This fact is due to the capability of bacteria to transmit and acquire resistance to drugs used as therapeutic agents. However, the problem of microbial resistance is growing, but the outlook for the use of antibacterial agents in the future is still unknown. A number of studies have reported the antibacterial activity of various plant extracts, which is due to the presence of phytochemicals synthesized in the secondary metabolism, and therefore suggested that the use of plant extracts with known antimicrobial properties can be of great significance in therapeutic treatments [26,27]. In the present

Table 3. Antibacterial activity of different extracts of *Ficus racemosa*

Name of bacteria	Zone of inhibition(mm)															
	MEFR			EEFR			CEFR			NEFR			PEFR			Std
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	D
S. aureus	17	15	12	16	14	11	13	10	7	13	10	8	15	13	10	29
S. pyogenes	15	12	9	14	11	9	13	10	8	12	9	7	15	13	10	28
B. cereus	15	13	9	15	12	9	13	10	9	14	10	9	16	14	11	27
B. subtilis	16	14	12	15	13	9	15	13	10	12	10	9	14	12	9	29
E. coli	15	11	10	14	12	8	14	10	9	12	10	8	16	12	10	28
S. typhi	14	12	9	13	10	8	8	5	NA	10	7	NA	14	11	8	26
S. dysenteriae	13	9	8	15	11	8	12	9	5	10	10	5	17	12	10	29
A. tumefaciens	16	14	11	15	13	11	14	12	9	15	11	10	13	11	9	31

Std= Azithromycin, A= 600 µg/ disc, B= 400 µg/ disc, C= 200 µg/ disc, D= 15 µg/ disc, NA= Not detected

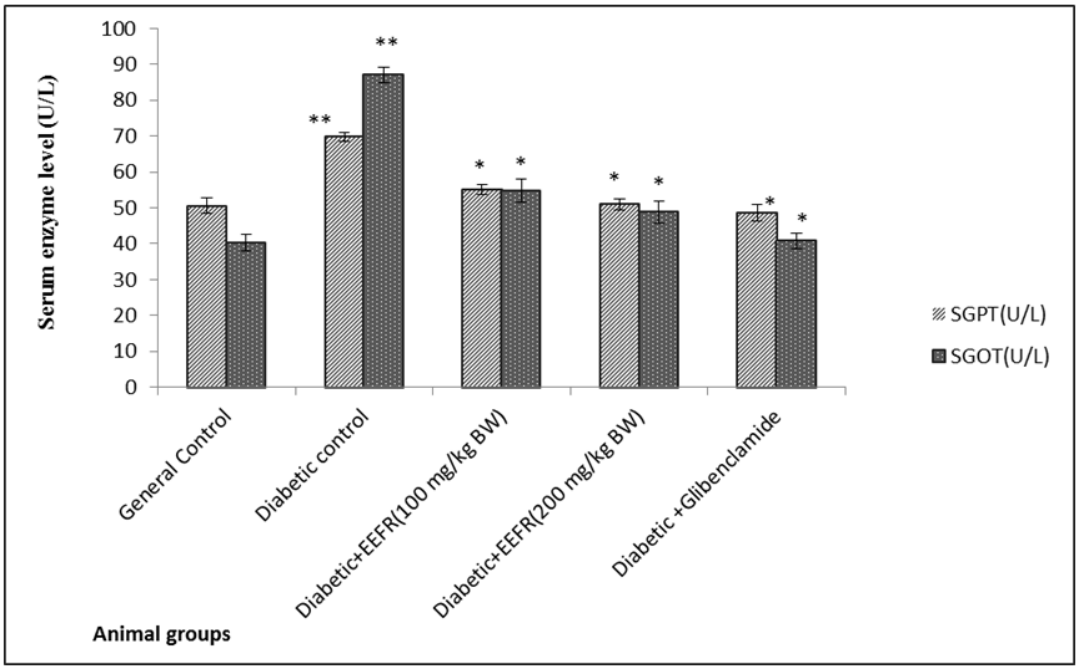

Fig. 1. Effects on SGPT and SGOT level after 21 days of treatment of ethanol extract of *Ficus racemosa*

The data are expressed as mean±standard deviation (n=6). **P<0.001 compared with normal control; *P<0.001 compared with diabetic control

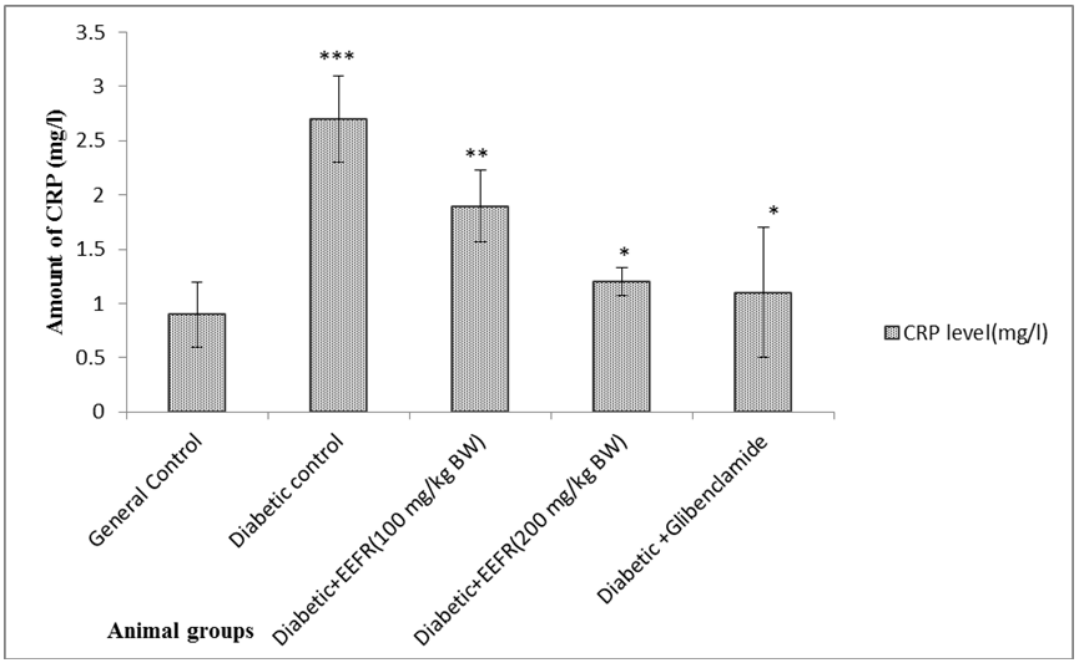

Fig. 2. Effects on CRP level after 21 days of treatment of ethanol extract of *Ficus racemosa*
*The data are expressed as mean±standard deviation (n=6). ***P<0.001 compared with general control; **P<0.05 and *P<0.001 compared with diabetic control*

study each extract of *Ficus racemosa* showed considerable broad-spectrum antibacterial activity against some pathogenic bacteria suggesting that it may be a promising source for the treatment of various infectious diseases. Since some active components can only be extracted by polar compounds, while some by less polar and yet some by non-polar compounds, therefore, different biological activity of plant extract largely depends on the type of solvent used in the extraction procedure. In the present study, methanol, ethanol and petroleum ether extract showed comparatively higher antibacterial activity than the other two extracts which is probably due to the large content of active compounds responsible for this property in the former three extracts. This finding suggests that methanol, ethanol or petroleum ether would be the preferable solvent for the extraction of phytochemicals responsible for antibacterial activity from this fruit.

The SGOT and SGPT levels are also increased in diabetic patient as an indication of the liver damage. Treatment with extract and glibenclamide significantly reduced their levels. CRP, a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease [28,29]. It has also been reported that serum CRP levels are elevated in patients with diabetes [30]. CRP level was significantly decreased along with the decrease of blood glucose and serum cholesterol during the treatment of the extract in diabetic mice.

5. CONCLUSION

From the findings of the present study it could be concluded that *Ficus racemosa* is an important source of potent pharmacological compounds. It could be used as an antibacterial agent to treat various infectious diseases. *F. racemosa* fruit might be used in the future as herbal medicine for the treatment of diabetes mellitus and cardiovascular disease (CVD) as it reduces the metabolic complications under diabetic condition.

Sometimes purified compounds demonstrate higher activity which recommends the isolation and identification of the active principles. To understand the synergistic effects, if any, of the constituents, purification is a must. Therefore, further studies are needed to identify the chemical constituent of *Ficus racemosa* responsible for these activities. This is an ongoing study and further work is being carried out to investigate its impact on molecular level.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Approval and permission of using mice model were obtained from the Institute of Biological Sciences, University of Rajshahi, Bangladesh.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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