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RESEARCH ARTICLE

Effect of *Ficus lacor* Buch. Ham. Fruit Extract on Dexamethasone Induced Insulin Resistant Rats

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ABSTRACT:
Fruits of plant *Ficus lacor* Buch. Ham. were evaluated for its antidiabetic efficacy in dexamethasone induced insulin resistant rats. Extraction of fruits was done by soxhlation method to get fruit extract. Acute toxicity study of fruit extract was performed as per OECD 425 guidelines using wistar rats. Rats weighing between 200 to 250 g were selected for experimental work and divided randomly in to five groups normal control, diabetic Control, standard control (metformin, 2mg/kg), fruit extract (200mg/kg), fruit extract (400mg/kg) with five animals in each group. Dexamethasone (10mg/kg s.c) was used to induce insulin resistance in wistar rats weighing between 200 to 250g for 11 days. Animals in treatment group were treated with metformin (40mg/kg), fruit extract (200 and 400mg/kg) for 11 days daily. At the end of 11 days study, different parameters like body weight, food intake, water intake, glucose, cholesterol, triglyceride, HDL, LDL, VLDL, urea, uric acid, creatinine, aspartate aminotransferase (AST) and alanine transaminase (ALT) were determined. Liver and muscle was isolated for estimation of glycogen level. The result indicates significant ($P < 0.05$) improvement in different biochemical parameters when compared with diabetic control group. The liver glycogen level was increased significantly ($P < 0.001$) when compared with diabetic control group. The antidiabetic effect of fruit extract of plant *Ficus Lacor* Buch. Ham. was found to be dose dependent.

KEYWORDS: *Ficus lacor* Buch. Ham., Dexamethasone, Antidiabetic, Lipid profile, Glycogen.

INTRODUCTION:
Diabetes mellitus (DM) is a group of diseases characterized by high blood glucose level as result of abnormal metabolism of carbohydrate, lipid and fats. It is caused by reduced insulin level or reduced sensitivity of insulin[1]. Type 1 diabetes mellitus also termed as insulin dependent diabetes mellitus is chronic disease characterized by either low insulin level or absence of insulin. Type 2 diabetes mellitus termed as non-insulin dependent diabetes mellitus is chronic disease characterized by reduced sensitivity of insulin which may be normal or reduced[2]. In last few years diabetes became one of the global health problem associated with many related complications. Presently as per World Health Organization (WHO) estimates about 176 million peoples are suffering from this chronic disease[3].

One of the major reason causing many deaths globally is complications associated with DM. The long-term diabetes mellitus may result into many micro and macro vascular complications and associated abnormality[4]. Treatment options available presently is based on use of allopathic drugs, diet planning, exercise etc. The allopathic drugs insulin and oral hypoglycemic are associated with some individual unwanted effects which makes them inconvenient for long term use[5]. Considering global incidence of DM and limited effective treatment options, presently use of natural remedies becoming more popular for long term treatment of DM. Presently many medicinal plants were proved scientifically effective and used practically for treatment of diabetes mellitus. Natural plant remedies are additionally considered to have fewer toxic effects and comparatively cost effective[6].

Traditionally used plant *Ficus Lacor* Buch. Ham. was used traditionally for treatment of some disorders like snake bite, arthritis, skin problems, inflammation. The

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plant *Ficus Lacor* Buch. Ham. is evergreen plant commonly known as plaksha[7,9]. It is also called by the name pitana, karpari or parkati in different regions. The active constituents present in the plant are long chain alcohols, sterols, beta sitosterol, lanosterol which make it useful for treatment of different disorders. Different parts of the plant like fruits, leaves, cork contains these active ingredients so these are used traditionally[8,9]. The other species of the plant *Ficus* were proved to have antidiabetic potential. Traditionally it is claimed fruits of plant were used for treatment of diabetes[5]. So, we made an attempt to prove the validity of traditional claim by investigating its probable antidiabetic potential by dexamethasone induces insulin resistance in wistar rats.

MATERIALS AND METHODS:

Chemicals:

Metformin was obtained from Yarrow Chem Products Ltd, Mumbai, India. Biochemical parameters were estimated using commercial estimation kits from Coral Clinical Systems, Goa, India. All chemicals used during study were of analytical grade.

Plant material:

Fresh fruits of plant *Ficus lacor* Buch. Ham. was collected from locality of Insuli, sawantwadi, Dist. Sindhudurg, Maharashtra, India in first week of May. Plant specimen was authenticated at Department of Botany, Shri. Pancham Khemraj Mahavidyalay, Sawantwadi, Maharashtra, India. Voucher specimen sample (Voucher No. 12-B/226/2020 1) was deposited at same place for further reference.

Plant material processing and preparation of extracts:

The fresh fruits of plant *Ficus lacor* Buch. Ham. were washed with tap water and shade dried, avoiding direct contact with sun light. Completely dried fruits were subject to mechanical grinding to get fruit powder. Extraction was carried out using Soxhlet apparatus in 72 h[10]. A semisolid extract was dried using rotary evaporator at 40°C and resultant extract was stored in airtight container at 2 – 8°C.

Experimental animals:

Adult Wistar rats of either sex (200-250g) were housed in animal house at appropriate temperature of (26±1°C) and light controlled (12 hr light: 12 hr dark) room. Animals were provided with food (Nutrivet Life Sciences, Pune, Maharashtra, India) and drinking water *ad libitum*. The study protocol was approved by the Institutional Animal Ethical Committee of Yashwantrao Bhonsale College of Pharmacy, Sawantwadi, India (Approval No: CPCSEA/IAEC/2019-20/01).

Acute oral toxicity study:

Acute oral toxicity of fruits of *Ficus lacor* Buch. Ham. was performed using adult wistar albino rats (200 - 250 g) of either sex maintained at standard conditions. Animals (n=5) were fasted overnight[11,12]. Animals were divided randomly in two groups control and test which received vehicle and fruit extract respectively. The dosing was started at 175mg/kg and continued up to 2000mg/kg as per the OECD 425 protocols. The animals were observed continuously for next 14 days, during this animal had not shown any toxicity, mortality and behavioural changes.

Experimental induction of diabetes:

Wistar rats weighing between 200 to 250g were selected in experimental study to induce insulin resistance. Dexamethasone induced insulin resistance was produced in wistar rats at dose of 10mg/kg by subcutaneous (s.c.) route administered daily for 11 days. Dexamethasone was dissolved in normal saline solution and resultant solution was injected subcutaneously to wistar rats for 11 days. The treatment was given to rats for experimental period of 11 days daily by oral route. Insulin resistance was developed within experimental period of 11 days confirmed by measuring blood glucose level on 11th day[13,14].

Experimental Design:

A total of 25 Wistar rats (5 normal and 20 Insulin resistant) were used in study. The rats were divided randomly in to five groups with five animals in each group.

Group- I: Normal control group (NC), receives 2 ml/kg 0.5% DMSO in distilled water,

Group- II: Diabetic control group (DC), receives dexamethasone 10 mg/kg and 2 ml/kg 0.5% DMSO in distilled water,

Group- III: Standard treatment group (STD), receives dexamethasone 10 mg/kg and metformin 40 mg/kg,

Group- IV: Fruit extract treatment group (FE200), receives dexamethasone 10 mg/kg and fruit extract 200 mg/kg,

Group- V: Fruit extract treatment group (FE400), receives dexamethasone 10 mg/kg and fruit extract 400 mg/kg.

Dexamethasone (s.c.) and all treatments (oral route) given daily for total 11 days.

On 11th day of study all overnight fasted animals were anesthetized using diethyl ether and blood sample was collected through retro orbital puncture method[15] and serum was separated by centrifugation of blood at 5000 rpm. Separated serum sample was used further for estimation of different biochemical parameters. Animals were sacrificed by cervical dislocation to dissect liver and skeletal muscle. Dissected organs were washed with ice cold saline and used for further experimental study.

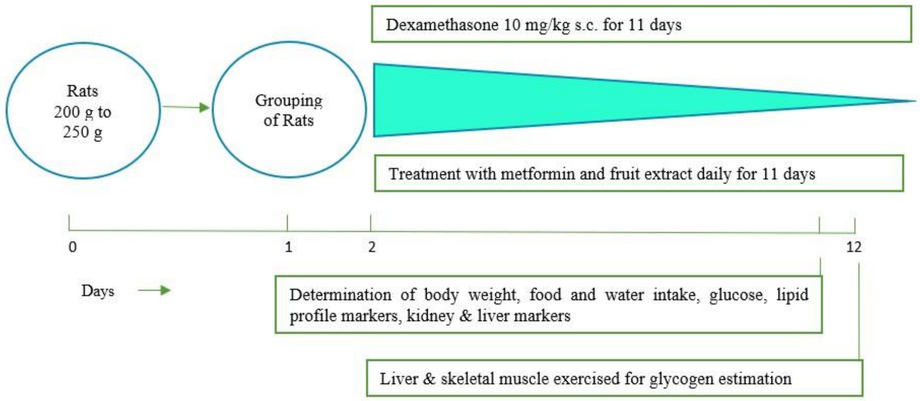

Figure 1: Experimental Scheme

Experimental Scheme:

Experimental sceheme for dexamethasone induced antidiabetic activity of fruit extract is presented in figure 1.

Blood glucose, body weight, food intake and water intake:

Fasting blood glucose, body weight, food intake and water intake were measured on 11th day of study.

Estimation of serum lipid profile markers:

The serum lipid profile markers cholesterol, triglyceride, HDL, LDL and VLDL were estimated using commercial kits.

Estimation of kidney and liver serum markers:

Fasting serum markers of kidney and liver like urea, uric acid, creatinine, AST and ALT were estimated using commercial kits.

Estimation of liver and skeletal muscle glycogen:

Skeletal muscle and liver tissue was digested with 30% KOH and precipitated with ethanol and further used for estimation of glycogen level by Hassid and Abraham method[16,17].

Statistical analysis:

The result obtained were expressed as mean±SEM (standard error of mean). The statistical analysis of the results was carried out by using analysis of variance (ANOVA) followed by Dunnett's test. A value of $P < 0.05$ was considered significant.

RESULTS:

Acute toxicity:

Acute toxicity study of fruit extract of *Ficus Lacor* Buch. Ham. Confirmed absence of toxic effects and mortality up to the dose 2000mg/kg as per OECD 425 guidelines. All animals when observed closely for 14 days had not shown any changes in skin, fur, eyes, mucous membranes, motor activity, respiratory and central nervous system parameters. The changes in body weight of animals were normal till end of study. This observation indicates the absence of toxicity of plant in experimental animals and safe for further use in experiment. The further study was accomplished using 200mg/kg and 400mg/kg p.o. of fruit extracts.

Effect of extract on blood glucose, Body weight, food intake and water intake:

The result reveled diabetic control group significantly ($P < 0.001$) increases blood glucose level on 11th day when compared to normal control group. In metformin treated group blood glucose level was reduced significantly ($P < 0.001$) to normal on 11th day. The study indicates fruit extract shows significant ($P < 0.001$) reduction in blood glucose level in dose (200mg/kg and 400mg/kg) dependent manner when compared with diabetic control group. At the end of 11th day fruit extract was found to more effective at 400mg/kg.

The result for fruit extract on the body weight during 11 days of treatment is shown in table 1. The diabetic rats exhibited significant ($P<0.001$) reduction in body weight after dexamethasone treatment when compared with normal control group. The treatment groups of standard drug and fruit extracts showed significant ($P<0.001$) improvement in the body weight when compared with diabetic control group. The effect of fruit extract on food intake and water intake revels that after 11 days of treatment food and water intake reduced significantly ($P <0.001$) to normal when compared to diabetic control rats. (Table 1)

Table 1: Effect on blood glucose, body weight, food intake and water intake for fruit extract of *F. lacor* Buch. Ham.

Group	Blood glucose (mg/dl)	Body Weight (gm)	Food Intake (gm)	Water Intake (ml)
Normal	85.38 ± 2.34	213.21 ± 2.42	10.13 ± 0.35	7.44 ± 0.35
Diabetic	150.99 ± 2.66 ^{f}	158.43 ± 2.85 ^{f}	15.53 ± 0.39^f	15.13 ± 0.48 ^{f}
STD	89.81 ± 2.99 ^{c}	213.26 ± 2.54^c	9.29 ± 0.46 ^{c}	7.15 ± 0.36 ^{c}
FE200	104.69 ± 3.04 ^{c}	186.27 ± 2.96^c	11.40 ± 0.36^c	10.61 ± 0.31 ^{c}
FE400	98.24 ± 3.08 ^{c}	196.23 ± 2.96^c	10.28 ± 0.45^c	8.58 ± 0.24 ^{c}

Values are expressed as mean±SEM (n=5), $^a p < 0.05$, $^b p < 0.01$, $^c p < 0.001$, when compared with diabetic control group; $^d p < 0.05$, $^e p < 0.01$, $^f p < 0.001$, when compared with normal control group

Effect of extract on serum lipid profile markers:

Table 2 represents effect of fruit extract on different lipid parameters like cholesterol, triglyceride, HDL, LDL and VLDL. In diabetic rat's total cholesterol level was increased (154.64±3.01) significantly ($P< 0.001$) in comparison with normal control rats. Daily treatment of diabetic rats with metformin and fruit extract for 11 day found to reduce total cholesterol level significantly ($P < 0.001$) when compared to diabetic control rats. Triglyceride level was elevated (131.06±2.33) significantly ($P < 0.001$) in diabetic control rats in comparison to normal control rats (72.91±2.77). Dose dependent significant ($P< 0.001$) reduction was reported in triglyceride level by fruit extract in comparison with diabetic control rats. Serum HDL level in comparison to normal rats was found to reduced significantly ($P < 0.001$) in diabetic rats. Treatment with metformin and fruit extract significantly ($P<0.001$) elevated serum HDL level in dose dependent manner. Serum LDL and VLDL level in diabetic control rats was elevated significantly ($P<0.001$) compared to normal control group. Treatment with fruit extract found to reduce LDL and VLDL level significantly ($P<0.001$) in comparison to diabetic rats. (Table 2)

Table 2: Effect of fruit extract of *Ficus lacor* Buch. Ham. on lipid profile makers

Parameter	Normal	Diabetic	STD	FE200	FE400
Cholesterol (mg/dl)	106.42 ± 3.53	154.64 ± 3.01 ^{f}	105.99 ± 3.1 ^{c}	122.44 ±3.24 ^{c}	112.15 ± 2.9 ^{c}
Triglyceride (mg/dl)	72.91 ± 2.77	131.06 ± 2.33 ^{f}	76.56 ± 2.91 ^{c}	94.29 ± 2.20 ^{c}	84.59 ± 2.74 ^{c}
HDL (mg/dl)	48.22 ± 1.74	34.48 ± 1.41 ^{f}	46.24 ± 1.36 ^{c}	43.4 ± 0.95 ^{c}	47.73 ± 1.37 ^{c}
LDL (mg/dl)	43.61 ± 2.67	93.95 ± 2.29 ^{f}	44.44 ± 3.93 ^{c}	60.18 ± 3.39 ^{c}	47.5 ± 3.60 ^{c}
VLDL (mg/dl)	14.58 ± 0.55	26.21 ± 0.47 ^{f}	15.31 ± 0.58 ^{c}	18.86 ± 0.44 ^{c}	16.92 ± 0.55 ^{c}

Values are expressed as mean±SEM (n=5), $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$, when compared with diabetic control group; $^{d}p<0.05$, $^{e}p<0.01$, $^{f}p< 0.001$, when compared with normal control group.

Effect of extract on kidney and liver serum markers:

Effect of fruit extract on different kidney and liver markers urea, uric acid, creatinine, AST and ALT is shown in table 3. Serum urea level in diabetic control (41.15±0.66) rats was increased significantly ($P<0.01$) compare to normal control rats (37.28±0.84). Treatment of diabetic rats with metformin significantly ($P < 0.05$) reduces elevated serum urea level when compared with diabetic control rats. Fruit extract treatment at 400 mg/kg significantly ($P<0.05$) reduces serum urea level while effect at 200mg/kg was found to be non-significant. Diabetic rats with elevated serum uric acid level when treated daily for 11 days with fruit extract reduced uric acid level significantly ($P<0.001$) in dose dependent manner. In diabetic control rat's serum creatinine level was increased significantly ($P<0.001$) compare to normal control rats. In metformin and fruit extract treated groups elevated serum creatinine was reduced significantly ($P<0.001$) compare to diabetic control rats. Serum AST level in comparison to normal (12.43±1.56) rats was found to increased significantly ($P <0.001$) in diabetic control (24.43±2.12) rats. Fruit extract at 200mg/kg and 400mg/kg dose reduces significantly ($P<0.001$) elevated AST level compare to diabetic control rats. Elevated serum ALT level in diabetic rats was found to reduced significantly ($P < 0.001$) by metformin and fruit extract treatment compared to diabetic control rats. (Table 3)

Table 3: Effect of fruit extract of *Ficus lacor* Buch. Ham. on kidney and liver biomarkers

Table 3: Effect of fruit extract of *Ficus lacor* Buch. Ham. on kidney and liver biomarkers

Parameter	Normal	Diabetic	STD	FE200	FE400
Urea (mg/dl)	37.28 ± 0.84	41.15 ± 0.66 ^{e}	37.88 ± 0.79 ^{a}	39.77 ± 0.74	38.32 ± 0.63 ^{a}
Uric Acid (mg/dl)	4.54 ± 0.15	7.32 ± 0.11 ^{f}	5.22 ± 0.20 ^{c}	5.91 ± 0.25 ^{c}	5.33 ± 0.24 ^{c}
Creatinine (mg/dl)	0.59 ± 0.04	1.44 ± 0.06 ^{f}	0.68 ± 0.03 ^{c}	0.96 ± 0.05 ^{c}	0.83 ± 0.04 ^{c}
AST (U/l)	12.43 ± 1.56	24.43 ± 2.12 ^{f}	12.53 ± 1.45 ^{c}	16.53 ± 1.76 ^{c}	14.56 ± 2.13 ^{c}
ALT (U/l)	13.45 ± 1.86	25.35 ± 2.24 ^{f}	14.86 ± 1.65 ^{c}	18.86 ± 2.35 ^{c}	16.53 ± 1.87 ^{c}

Values are expressed as mean±SEM (n=5), $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$, when compared with diabetic control group; $^{d}p < 0.05$, $^{e}p < 0.01$, $^{f}p < 0.001$, when compared with normal control group

Estimation of liver and skeletal muscle glycogen:

Result revels significant ($P < 0.001$) reduction in liver glycogen level in dexamethasone diabetic control rats when compared with normal control rats. Treatment with fruit extract improved significantly ($P < 0.001$) liver glycogen level when compared with diabetic control rats. In skeletal muscle also same effect was observed, fruit extract was found to increase significantly ($P < 0.001$) reduced muscle glycogen level to normal in dose dependent manner during 11 days of treatment. (Table 4, Figure 2)

Table 4: Effect of fruit extract of *Ficus lacor* Buch. Ham. on liver and skeletal muscle glycogen

Group	Mean Glycogen level (mg/g of tissue)	
	Liver	Skeletal Muscle
Normal	62.35 ± 1.58	35.35 ± 1.65
Diabetic	35.46 ± 2.32 ^{f}	19.65 ± 2.05 ^{f}
STD	61.56 ± 1.45 ^{c}	35.64 ± 1.45 ^{c}
FE200	50.86 ± 2.45 ^{c}	30.65 ± 1.35 ^{c}
FE400	57.65 ± 1.68 ^{c}	34.65 ± 1.48 ^{c}

Values are expressed as mean±SEM (n=5), $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$, when compared with diabetic control group; $^{d}p < 0.05$, $^{e}p < 0.01$, $^{f}p < 0.001$, when compared with normal control group

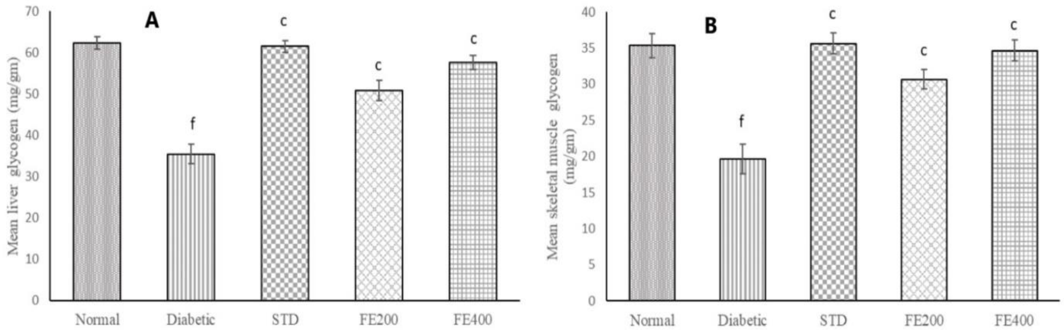

Fig. 2: Effect of fruit extract of *Ficus lacor* Buch. Ham. on A. Liver Glycogen, B. Skeletal Muscle Glycogen. Values are expressed as mean±SEM (n=5), $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$, when compared with diabetic control group; $^{d}p < 0.05$, $^{e}p < 0.01$, $^{f}p < 0.001$, when compared with normal control group

DISCUSSION:

Present allopathic drugs are having their own restrictions in its long-term use[18]. The scientists are searching for the plant oriented natural antidiabetic drug which can be used safely for long term[19,20]. Present era also gaining more consideration for searching natural drug which may reverse or protect from diabetic complications. Traditionally fruits of plant *Ficus lacor* Buch. Ham. were used for treatment of diabetes mellitus and it is proved to have antioxidant activity so present study was undertaken to evaluate antidiabetic potency of fruits of plant *Ficus lacor* Buch. Ham.

Acute toxicity study performed to assess the safety of natural products to be used in animals. As wistar rats and humans are having close anatomical and physiological relativeness so animal toxicity results can be extrapolated to humans[21]. The acute toxicity study as per OECD 425 guidelines revels there was no toxic effect of extract on different parameters observed closely. This indicates that LD50 of fruit extract might be above 2000mg/kg and it can be used safely below this dose. In present study type 2 diabetes induced by continuous administration of dexamethasone for 11 days. Hyperglycemia may be produced by dexamethasone through its ability to reduce secretion of insulin or increases insulin resistance. Glucocorticoids are used as short-term steroid therapy for diseases like acute gout, pulmonary obstructive diseases, in chemotherapy. It is also preferred during organ transplantation as immunosuppressant[22]. When it is used to induce diabetes, may act by increasing glucose synthesis in liver, increasing insulin resistance and decreasing insulin secretion. The overall effect of dexamethasone is elevated blood glucose level resulting in to type 2 diabetes mellitus[23].

Fruit extract when administered for 11 days in dexamethasone induced insulin resistant rats significantly reduces elevated blood glucose level. The effect might be due to reduced insulin resistance in diabetic rats which increases the glucose uptake in target organs. The improved insulin sensitivity may increase overall effect of insulin on different target organs resulting in to reduced blood glucose level in diabetic rats. In diabetic rats reduced body weight was observed as a result of insulin resistance causing hyperglycemia. In diabetic rats as insulin resistance was developed it resulted in to elevated blood glucose level. This may attribute to increase in metabolic reactions to generate new glucose by gluconeogenesis from protein and lipids. Increase in metabolic reactions results in to weight loss. Weight loss can activates feeding center and increase in food intake in diabetic rats[24]. As result of hyperglycemia osmotic pressure of urine is increased and net loss of urine is increased. Increased urine loss causes excessive water loss from body resulting in to excessive thirst and increased water intake[25]. As fruit extract of plant reduces significantly blood glucose level to normal resulting in to increased body weight, reduced food and water intake.

In diabetic rats due to increased insulin resistance results in to increase in metabolism of lipids. Increased lipid metabolism elevates blood cholesterol, triglyceride, LDL, VLDL and reduces HDL level. Dyslipidemia may result in to further diabetic micro vascular and macro vascular complications. Fruit’s extract exhibited significant effect on normalizing lipid profile which may avoids further related complications[26]. Elevated level of urea, uric acid and creatinine was reduced significantly by fruit extract in dexamethasone induced diabetic rats. Urea, uric acid and creatinine level may be increased as a result of increased insulin resistance and probable damage in kidney through which it is eliminated[27].

Elevated AST and ALT level indicates the probable liver toxicity. The insulin resistance may increase serum AST and ALT level indicting impaired lever function. Treatment with metformin and fruit extract reduces elevated AST and ALT level might be due to protective effect on liver resulted from increased insulin sensitivity[27,28]. The effect of fruit extract on liver and skeletal muscle glycogen level was increased significantly when compared with diabetic control group. The liver and muscle glycogen level improvement may be accomplished by reduced resistance of insulin which makes the glucose to move (increase in glucose uptake) in to these organs.

CONCLUSION:

In present study traditional claim for antidiabetic potential of plant *Ficus lacor* Buch. Ham. can be justified. Fruit extract exhibited significant reduction in blood glucose level in diabetic rats. The fruit extract of plant *Ficus lacor* Buch. Ham. was found to increase body weight, reduce food intake and water intake. Kidney and liver biochemical parameters were normalized with the used of fruit extract in diabetic rats. The liver and skeletal muscle glycogen level was improved significantly in diabetic rats by fruit extracts. These results prove effectiveness of plant *Ficus lacor* Buch. Ham. as alternative for management of diabetes mellitus.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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