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Research Article

Therapeutic Effect Of *Jatropha Multifida* Linn. Ethanol Extract And Its Fraction On High Fat Diet And Streptozotocin Induced Diabetic Nephropathy In Rats

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ABSTRACT

The present investigation has been carried out on leaves of Jatropha multifida Linn. The effect of ethanol leaf extract (JMEE) and its hexane fraction (JMHF) were investigated in HFD and STZ (40 mg/kg) induced diabetic rats and its histopathological study in the kidney tissues. Under histopathological analysis, the diabetic rat's proximal convoluted tubules showed tubular necrosis with loss of their brush boundary, glomerular enlargement, interstitial space infiltration by lymphocytes, and thickening of the basement membrane. Jatropha multifida extracts lowered blood glucose level. While out of the two, maximum reduction was seen in JMHF at 200 mg/kg. The result of the present study is also justified by histopathological examinations of the kidney. This may be due to the active phytoconstituents isolated from the fraction of the 50% ethanol extract of the leaves. Phytochemical analysis of extract and fraction indicated high concentrations of flavonoids, phenolic acid and saponins. The kidney of the diabetic rats was observed to nearly return to its normal histological architecture after treatment with JMHF and can therefore be employed as a substitute medication to treat Type 2 diabetes and associated nephro-complications.

INTRODUCTION

Diabetes is a metabolic disorder with severe repercussions for an individual's well-being. It is now known to be the primary cause of long-term renal failure, with many diabetics developing end-stage renal disease and needing dialysis or organ replacement. Diabetes mellitus (DM) can lead to significant consequences, one of which is diabetic nephropathy (DN)[1]. Histologically, DN causes kidney injury that is characterized by tubular epithelial degeneration, podocyte loss, macrophage infiltration, thickening of the glomerular basement membrane, and mesangial

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matrix enlargement[2,3]. Furthermore, oxidative stress is caused by an imbalance between oxygen-derived radicals and the organism's antioxidant capacity. This causes oxidative damage to lipids, proteins, and nucleic acids. There have been reports that hyperglycemia in DM might cause oxidative stress, inflammation, fibrosis, and renal apoptosis[4]. More focus has recently been placed on oxidative stress as the primary cause of DN[5,6]. Genetic predisposition, elevated glucose, RAAS activation, reactive oxygen species, activation of the protein kinase C pathway, elevation of advanced glycation end-product (AGE), and glomerular hyperfiltration are some of the variables associated with diabetic ketoacidosis[7]. Currently, Insulin and oral medicines are just two of the strategies utilized to control diabetes[8,9]. However, certain treatments do have unfavorable side effects. Thus, further research is needed to develop safer and more effective anti-diabetic medications. Jatropha multifida Linn. often designated as “coral bush” is a species of Jatropha, belongs to the family Euphorbiaceae, is an endogenous plant to Tropical Americas but now extensively grown for its attractive plants and flora in Tropical to sub-tropical areas across the world. Parts of this plant are shown in Figure 1. It is easily disseminated by seeds or cuttings [10]. It is reported to contain polyphenols, flavonoids, tannins, terpenoids, alkaloids and saponins that possess anti-microbial, wound healing, anti-diabetic, anti-inflammatory and anti-oxidative properties[11, 12, 13, 14, 15,16]. Phenolic acids such as vanillic, cis and Trans ferulic, p- OH Benzoic acid, phloretic acids and glycoflavones and Flavonoids determined as Vitexin and Isovitexin have been reported in this plant. Consequently, it is sense to assume that antioxidants will play a major role in reducing the symptoms associated with diabetes. J. multifida leaf extracts have garnered attention for their remarkable antioxidant capabilities, mostly because of the presence of substances including quercetin, kaempferol, and luteolin[15]. For example, luteolin is well known for its ability to restore antioxidant functions in kidney cells, protecting against oxidative stress[17]. Despite of this herb being used in the treatment of hyperglycemia, currently there is lack of evidence on its role in ameliorating nephro disease in DM. This study was aimed to investigate effects of JM on kidney function, kidney histopathological changes, kidney oxidative, fibrosis, inflammatory and apoptosis in DM.

Figure 1. Aerial Parts And Leaf Of Jatropha Multifida Linn.

MATERIALS AND METHODS

Plant Material

Fresh leaves of J. multifida were collected from United Institute of Pharmacy, Prayagraj and were identified by Botanical Survey of India, Prayagraj (Approval No.-BSI/CRC/2021-22/435).

Animals

Adult Wistar rats (200-250gm) were taken from CPCSEA registered Laboratory Animal Supplier m/s Chakraborty Enterprises Kolkata (Registration No.- 1443/PO/Bt/S/11/CPCSEA). All rats were shifted to quarantine area for acclimatization to animal house for two weeks before the experiment. Rats resided in a control vivarium with food and water, maintaining a proper light and dark cycle. The experimental protocol was approved by the IAEC committee with Approval no. UIP/IAEC/Nov.-2021/04.

Extraction And Fractionation Of The Plant Leaves

The fresh leaves were thoroughly washed with tap water and air dried under shade at room temperature for 7 days and pulverized into coarse powder. 500 gm of the leaves were defatted using 3L of Petroleum ether by means of hot percolation and the marc obtained was dried in air and then extracted with 50% aqueous ethanol in Soxhlet apparatus. The obtained filtrate was stored in air tight container for future use. The filtrate obtained was successively fractionated using separating funnel with the following solvents in order of increasing polarity viz. n-hexane, chloroform, ethyl acetate, butanol and methanol (Figure 5). These extracts were further subjected to phytochemical testing.

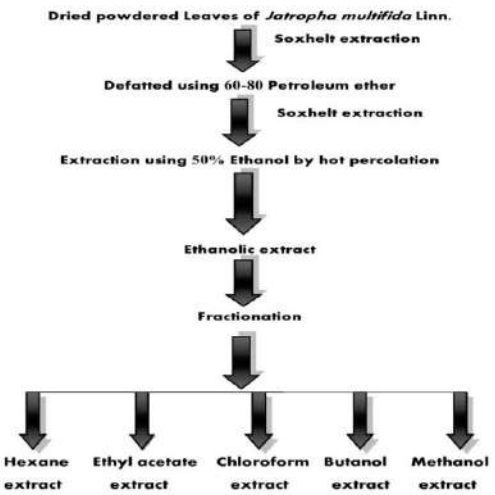

Figure 2. Extraction And Fractionation Of Jatropha Multifida Leaves

Detection Of Phytochemicals

The extract and fractions of J. multifida leaves were subjected to various phytochemical Screening to find out different phytoconstituents.

Pharmacological Studies

Oral Acute Toxicity Test (LD50)

This study was conducted in animals according to OECD guidelines 423. No toxicity and death was recorded. This estimates the safe use of leaves of Jatropha multifida.

Development Of HFD

The diet was freshly prepared in the laboratory every 3rd day. Fat enriched diets have been popularly used to model obesity, dyslipidemia. Diet rich in fats easily induce type II diabetes. HFD brings about hyperinsulinemia, resistance of

insulin and intolerance of glucose[18,19]. High fat diet was tested by Food Analysis & Research Laboratory, University of Allahabad. The amount of protein, fat and total sugar present in the diet was 7.38, 37.17 and 15.20 g/100g. High fat diet was given for 12 days for the induction of type 2 diabetes with the help of low dose streptozotocin and HFD was continued till the end of the experiment. List of ingredients required to make HFD are given in Table 5.

Table 1. List Of Ingredients Used To Make HFD

Ingredients	Quantity (gm)
Crushed normal diet	300 gm
Vegetable ghee	450 gm
Sugar	150 gm

Induction Of Diabetes Mellitus

On 13th day, diabetes was induced by intraperitoneal injection of STZ dissolved in citrate buffer at low dose (40 mg/kg) followed by 10% fructose solution given orally for two hours. On 16th day, fasting BGL was measured using One Touch Glucometer. Rats with BGL above 200 mg/dL were used for the study.

Dose Preparation

Suspension of JMEE and JMHF were prepared by triturating the extracts with 2% gum acacia in mortar pestle separately. Doses of JMEE were given at 200 & 400 mg per Kgbw while JMHF at doses of 100 & 200 mg per Kg.

Treatment Protocol

The diabetic rats were divided into seven groups (n=6/groups). Experimental protocol is given in Table 6. Experimental design has been followed as per Magalhães [20] which is shown in Figure 6.

Table 2. Experimental Design And Procedure

Groups	Diet	STZ Induced	Treatments
Group I (Normal Control)	No Diet	No STZ	Normal Saline (NS)
Group II (Diabetic Control)	HFD	STZ	NS
Group III (Standard drug treated)	HFD	STZ	Metformin 100mg/kg
Group IV (Ethanol extract- Low dose)	HFD	STZ	JMEE (200 mg/kg)
Group V (Ethanol extract-High dose)	HFD	STZ	JMEE (400 mg/kg)
Group VI (Hexane fraction-Low dose)	HFD	STZ	JMHF (100 mg/kg)
Group VII (Hexane fraction- High dose)	HFD	STZ	JMHF (200 mg/kg)

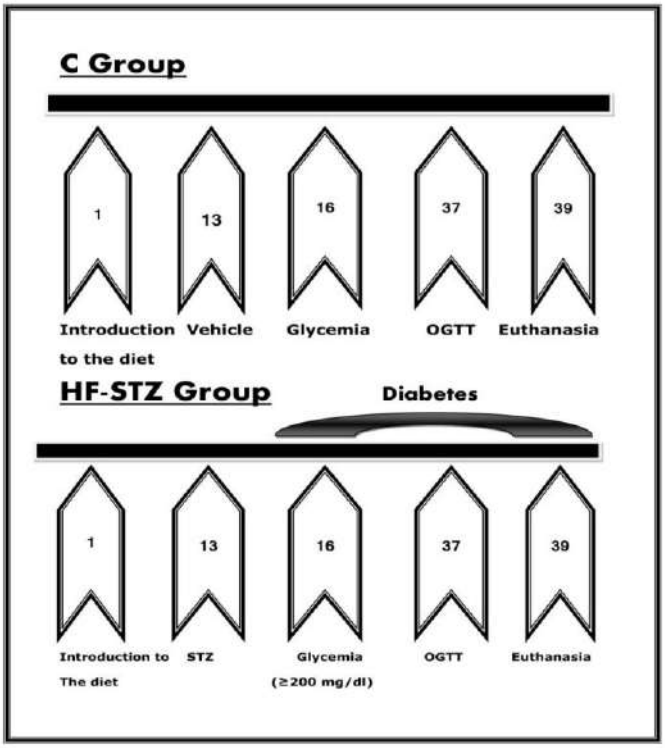

Figure 3. Experimental Design

Analysis Of Blood Sugar Level

Blood samples were collected at the intervals of 16th, 23rd, 30th, 37th and 39th day. On 39th day, blood sample was collected through retro bulbar route in blood collecting tube. Histopathological study was done at United Diagnostic, Prayagraj, Uttar Pradesh.

Body Weight Measurement

Body weight measurement was taken at 1st, 13th, 16th, 23rd, 30th, 37th and 39th day using weighing balance.

Statistical Analysis

Data obtained were analyzed using Two Way ANOVA (Version 9.3.1) software and expressed as mean±SD followed by Dunnet's t-test. Differences between means were regarded statistically significant below $p < 0.05$.

Histopathology Of The Kidneys

On 39th day of the experiment, the experimental rats were sacrificed by cervical dislocation method. Rats were dissected and kidney was taken out and stored in 10% formalin for histopathological evaluation. The sections were stained with haematoxylin /eosin dye using a routine protocol and examined at 40X using microscope.

RESULTS

Percentage Yield Of Extract And Its Various Fractions

The extract obtained through ethanol extraction and its fractionation were evaluated for percentage yield[21]. Percentage yield of the ethanol extract and its various fractions are mentioned in Table 1.

Table 3 Percentage Yield Of Extract And Its Various Fractions

Extracts	Percentage yield
Ethanol extract	11%
Hexane fraction	39.4%
Chloroform fraction	6%
Ethyl acetate fraction	1.8%

Butanol fraction	1.6%
Methanol fraction	1.5%

Phytochemical Tests

Phytochemical screening of the extract and fractions of J. multifida showed the presence of various chemical constituents. Saponins, tannins, phenolic acids, flavonoids, alkaloids are conspicuously present in large amount. Table 2 represents the result of various phytochemical tests performed.

Table 4. Phytochemical Analysis Of Jatropha Multifida Leaves Extract

Tests performed		Ethanol extract	HF	CF	EAF
Alkaloid	Mayer's Test	++	+	-	-
	Dragendorff's Test	+	+	+	++
Saponins	Foam test	++	++	++	+
Flavonoids	Sulphuric Acid	+	++	+	++
	Lead acetate test	+	+	+	+
	NaOH	++	++	+	
Phenols	$FeCl_3$	+	++	+	+
	Acetic acid sol.	++	++	++	+
	Dilute HNO_3	+	+	+	+

(+) Presence; (-) Absence; (++) Abundance

Acute Toxicity Test

It was performed according to OECD guideline 423[22]. Animals were orally administered with JMEE and hexane fraction (JMHF) of the Jatropha multifida leaves at various doses 5, 50, 300 and 2000 and 5000 mg/Kg, separatively. No death or toxicity was recorded for both JMEE and JMHF.

Effect Of The JMEE And JMHF On Blood Glucose Level Of Glycemic Rats

The effect of ethanol extract and its hexane fraction on the BGL of glycemic rats is presented in Figure 2. Therapeutic intervention of diabetes is aimed at reducing or avoiding elevations in glucose level of blood using hypoglycemic agents or insulin. Both the ethanol extract and its hexane fraction showed significant decrease in BGL. BGL in active fraction of J. multifida ethanol extract was observed to reduce effectively as the study duration increases while the untreated glycemic rats showed geometric increase in BGL with increase in study duration. Table 3 shows the result of treatment of various doses of the extract.

Table 5. Effects Of Jmee And Jmhf On Blood Glucose Level Of Blood In Hfd And Stz-Induced Diabetic Rats

Treatment	16th day (mg/dL)	23th day (mg/dL)	30th day (mg/dL)	37th day (mg/dL)	39th day (mg/dL)
Normal Control	98.1±3.6	96.8±2.4	96±2.7	95±2.8	94.5±3
Diabetic Control	242±3.3	250.6±3.2	258.3±3.1	271±2.3	273.5±2.2
Metformin 100 mg/kg	241.1±2.4	$176.3\pm3.2^{a,f}$	131.6±3.9	105±2.5	103.1 ± 2.8^{f}
JMEE 200 mg/kg	242.8±2.7	209±4.4	163.6±3	132.1±4	126.5±1.7
JMEE 400 mg/kg	246±3.2	195.3 ± 1.9^{a}	$150.3\pm2.3^{a,b}$	120.5 ± 1.7^{b}	$117.5\pm1.7^{a,b}$
JMHF 100 mg/kg	251.1±2.5	192.5 ± 1.7^{a}	145.8 ± 2.6^{a}	116.5±1.7	110.1 ± 3.1^{a}
JMHF 200 mg/kg	249.6 ± 2.1^{b}	181 ± 2.3^{b}	$135\pm2.8^{a,b}$	$108\pm3.5^{a,b}$	105 ± 2.5^{b}

Mean ± SD (n=6) Statistical significance in comparison to group II is ap<0.0001 and group III is bp<0.0001 while fp<0.0001 as compared to normal control.

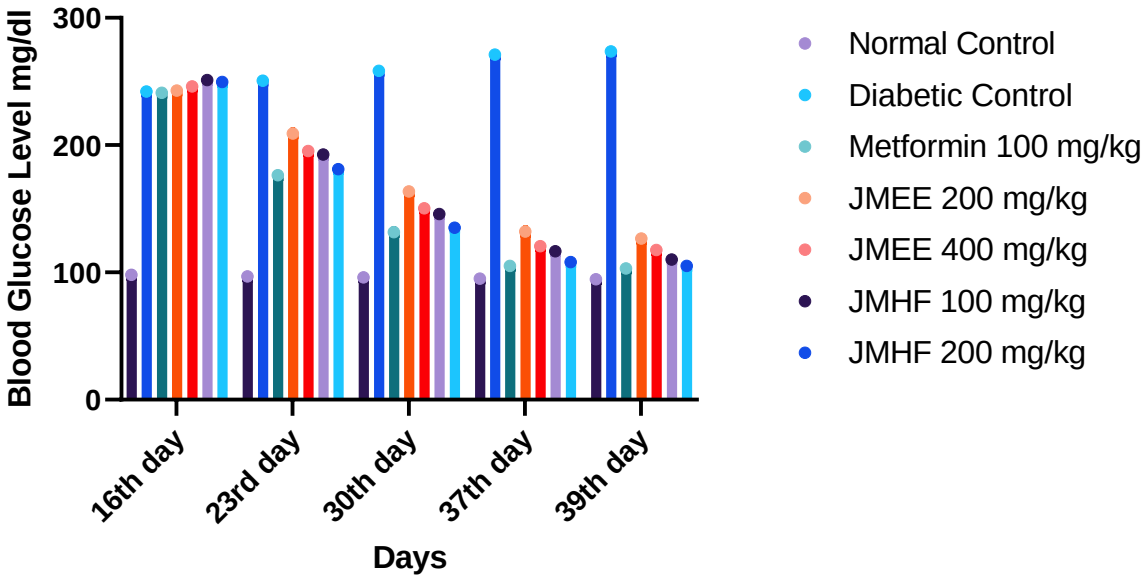

Figure 6. Graph Representing Blood Glucose Level In Diabetes Induced Experimental Animals

Effect Of The JMEE And JMHF On Body Weight

HFD and STZ induced diabetes significantly reduces body weight of the diabetic untreated rats as the study duration increases as compared with diabetic and normal control rats (Table 4). Diabetes is accompanied with increased lipolysis, gluconeogenesis, glycogenolysis and all of these biochemical activities result in muscle wasting and loss of tissue protein. Jatropha multifida is seen to prevent such changes by restoring body weight of the diabetic treated rats. Findings showed that the oral administration of Metformin (100 mg per Kg), JMEE (200 and 400 mg per Kg), JMHF (100 & 200 mg per Kg) to diabetic rat is improved. Treatment with ethanol extract in rats has shown prominent results in restoring body weight but the effects were more pronounced with JMHF (Figure 3). This improvement may be due to control in hyperglycemic condition.

Table 6. Effects Of Jmee And Jmhf On Body Weight Of Rats

Groups	16th day	23rd day	30th day	37th day	39th day
Normal Control	147.6±4.6	163.1±3.4	179.5±3.3	192.5±3.2	195.6±3.2
Diabetic Control	125.5±2.6	115.3±2.5	109±2.1	96.5±1.7	95.5±2.5
Metformin 100 mg/kg	120±3.2	142.1±3.4[b]	147.6±3.7[b,f]	153.1±3.8[a,f]	155±2.6[b,f]
JMEE 200 mg/kg	130±1.2	132±2.1[c]	138.8±1.7	142.3±2.3	143±2.5[c]
JMEE 400 mg/kg	133.5±2.2[a]	140.5±2.9	146±2.3	151.3±2.4[b]	152.8±2.1
JMHF 100 mg/kg	130.5±4	144.3±3.3	149±3.8	156±4.7	157±3.6
JMHF 200 mg/kg	132.3±2.8[b]	151±3.4[c]	154±5.1[b]	161±3.4[d]	162±5.6[b,d]

Mean ± SD (standard deviation) for 6 experimental animals in each group. Statistical significance in comparison to Diabetic Control (ap<0.001) and (bp<0.0001) and cp<0.0001 and dp<0.01 as compared to Metformin while fp<0.0001 as compared to normal control.

Histopathological Assessment Of Kidney

Group I shows that glomeruli appeared normal with normal renal corpuscles, central veins, sinusoids with tubules being lined by single layer of cuboidal cells (Figure 4). Deformity of renal corpuscles, atrophy of glomeruli capillaries with perivascular edema, fibrosis were seen in Group II. The normal architecture was restored to the same as that of normal control in Group III. Central veins, portal triads and sinusoids appeared normal.

Group IV shows degenerated cytoplasmic regions with mild edema, fibrosis and infiltration by lymphocytes, plasma cells and glomeruli. The normal architecture was restored similar to Group III treated kidney in Group V. Moderate increase in mesangial cellularity and matrix was seen. Histopathological examination of Group VI shows mild edema with normal glomeruli. The tubules represent cloudy swelling of the columnar cells. Minutely examined Group VII shows normal corpuscle and glomeruli with marked protection against diabetic changes.

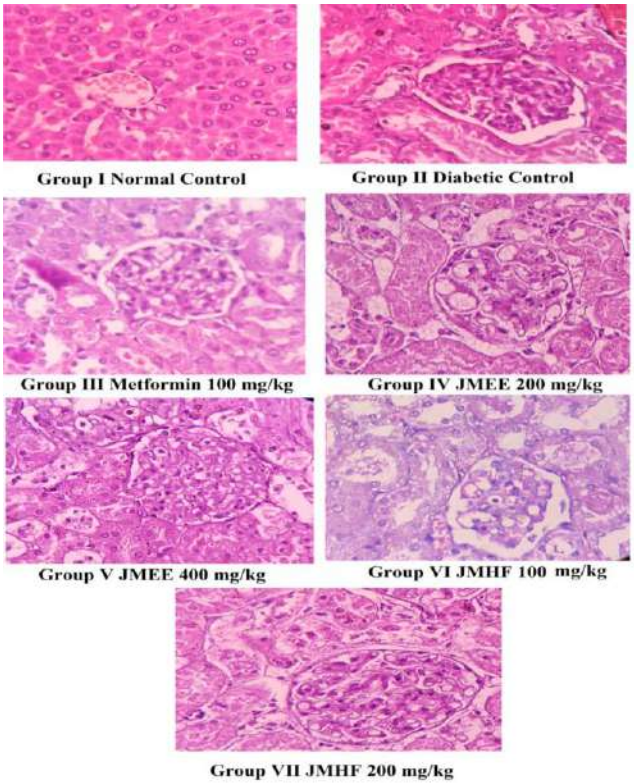

Figure 7. Histopathology Of Kidney

DISCUSSION

Leaves of Jatropha multifida has shown to be a potential agent for the treatment of DM, restoration of body weight and improvement of renal profile of diabetic treated rats. Thus, having a protective role on complications associated with diabetes which may be due to the presence of flavonoids, saponins or phenolic acids. Treatment with Jatropha multifida was found to almost restore the normal histopathological architecture of kidney of STZ-induced diabetic rats. Additional research is being conducted to identify and characterize the active ingredient and to better understand the mechanism underlying the anti-diabetic action. This study suggests that extract of Jatropha multifida besides its hypoglycemic activity can prevent the kidney impairment caused by diabetes. Many studies have also reported the relationship of sex hormones with the progression of Diabetic renal disease. However, the exact mechanism remains unclear[23,24]. Results of this study showed that treatment with J. multifida extract can protect the kidney tissue against tissue damage which is induced by oxidative stress related to diabetes. Increasing the number of glomeruli in diabetic rats may be due to the presence of antioxidant compounds of the plant[25,26] . Nevertheless, more research on J. multifida is required in order to determine the active principles underlying its nephroprotective effect in diabetes, as per our findings.

CONCLUSION

The study's data demonstrated that, in contrast to the greatly raised blood glucose levels in the diabetic control rats, JMHF had significant antihyperglycemic action that may return the blood glucose levels of diabetic rats to nearly normal. Additionally, the research revealed that untreated DM might cause hyperglycemia in diabetic rats, as well as decreased renal functioning and dyslipidemia. JMHF treatment significantly reduced the negative effects of diabetes on body weight and haematological markers in diabetic rats. These results imply that JMHF therapy could improve the physiological and biochemical processes in a diabetic state, which may be essential for the management of diabetes.

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AUTHOR CONTRIBUTIONS:

Concept – S.S.; Supervision – S.T.; Resources – S.T.; Materials – S.S., S.T.; Data Collection and / or Processing – S.T., S.S.; Analysis and/or Interpretation – S.S.; Literature Search – S.S., S.T.; Writing – S.S., S.T.; Critical Reviews – S.T.

CONFLICT OF INTEREST STATEMENT:

The authors declared no conflict of interest.

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