Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Ethanolic Extract of *Momordica dioica* Roxb. Leaves Show Potent Anti-diabetic Activity on Experimental Wistar Albino Rats

Pradeep Adlak[1], Rakesh Sagar[2], Mohan L. Kori*[1]

[1]*Vedica College of B. Pharmacy, RKDF University, Bhopal, Madhya Pradesh, India*
[2]*Shri G. S. Institute of Technology and Science, Indore, Madhya Pradesh, India*

ARTICLE INFO

Article history:
Received: 28 August, 2022
Revised: 09 September, 2022
Accepted: 13 September, 2022
Published: 30 September, 2022

Keywords:
Diabetes, *Momordica dioica*, Streptozotocin Glycosylated hemoglobin, Antioxidant.

DOI:
10.25004/IJPSDR.2022.140518

ABSTRACT

Diabetes mellitus is one of the most common endocrine metabolic disorders and significantly impacts the health, quality of life, and life expectancy of patients as well as on the healthcare system. Herbal remedies are convenient for managing diabetes due to their traditional acceptability and availability, low cost, and fewer side effects. The study aimed to evaluate the anti-diabetic effects of ethanolic extract of Momordica dioica leaf in normal and streptozotocin (STZ)-induced diabetic rats. In the study, two doses of ethanolic extracts of *Momordica dioica* leaf (MDL) were administered to normal rats for an oral glucose tolerance test. For anti-diabetic studies in STZ-induced diabetic rats, the effects of extracts were observed for duration of 28 days for blood glucose alterations. After the completion of the experimental period, the experimental rats were sacrificed and the collected serum samples were subjected to various biochemical parameter studies, including lipid profile, glycosylated hemoglobin (HbA1c), urea, and creatinine level studies. Whereas the tissues collected were subjected to antioxidant studies followed by histopathological studies of the pancreas. In this research study, it was observed that the MDL extracts showed a significant reduction in blood glucose level, reverted the altered lipid profile, and increased HbA1c to normal. It significantly normalized the urea and creatinine levels, as well as levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH). Thus, from this study, it could be concluded that MDL extract exhibited potent anti-diabetic activity in STZ-induced diabetic rats. This significant activity may be due to the presence of gallic acid, rutin, charntin, ferulic acid, and ellagic acid.

Introduction

Diabetes mellitus (DM) is the most common metabolic disorder that leads to high blood glucose due to a lack of the hormone insulin.[1] It may be due to degenerative changes in β-cells in the pancreatic islets, reduced effectiveness of the hormones due to the formation of anti-insulin antibodies or inactive complexes, immune-mediated islet cytotoxicity, or inappropriate secretion of hormones by neoplasm in other endocrine organs.[2] It is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental factors, resulting in abnormally high blood sugar levels. These deficiencies or insensitivity cause glucose to accumulate in the blood, leading to various complications like blindness, kidney failure, heart attacks, strokes, and lower limb amputation. According to the WHO, diabetes was the 9th leading cause of death among 1.5 million people in 2019. It is estimated that the global diabetes prevalence will rise by 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[3] Out of the four types of diabetes, type 2 accounts for over 85% of cases worldwide. Currently, the available therapy for diabetes includes a range of oral hypoglycemic agents, but they are reported to produce serious adverse side effects.[4] For a long time, herbal medicines have been a highly esteemed source of medicine. Therefore, they have become an important part of modern and high-tech medicines.[5] In the present condition, the demand for drugs of natural

***Corresponding Author:** Dr. Mohan L. Kori

Address: Vedica College of B. Pharmacy, RKDF University, Bhopal, Madhya Pradesh, India

Email ✉**:** mohanlalkori@gmail.com

Tel.: 9893968611

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

origin had increased due to their fewer side but more safe effects on diabetes mellitus.

Momordica dioica Roxb, is a creeper that climbs, known as kakora in Hindi, and belongs to the Cucurbitaceae family. Its fruit, leaves, and tuberous roots are used as a folk remedy for diabetes mellitus in India.[6] Leaves are aphrodisiac, anthelmintic, cure tridosha, fever, asthma, bronchitis, high cough, piles, jaundice, asthma, hepatic damage, mental digestive disorders, bleeding piles, bowel affection and urinary complaints. The juice of the leaves is mixed with coconut, pepper, red sandalwood, and to form an ointment and applied to the head to relieve pain in the head.[7,8]

Fruits of *M. dioica* have already been reported for anti-diabetic potential.[9] Research studies showed the presence of phytoconstituents like alkaloids, proteins, amino acids, phenolic compounds, glycosides, saponins, triterpenoids, and flavonoids in the leaf.[10] Further, the major components reported in leaves were gallic acid, rutin, ferulic acid, charntin and ellagic acid.[11] According to ethnobotanical claims, the leaves are used for the treatment of jaundice and other hepatic diseases by the folk tribes of India.[12] As per our exhaustive literature review, there is no scientific report published in support of the anti-diabetic activity of *M. dioica* leaves.

Therefore, to analyze the traditional claims, research was conducted to assess the anti-diabetic effect of *M. dioica* leaves using streptozotocin-induced rats.

Based on the literature on toxicity studies on leaves, they are considered safe,[13] hence leaf part was chosen for the detailed anti-diabetic studies.

Materials And Methods

Materials

Streptozotocin (Sigma Aldrich, Bangaluru, India), glibenclamide (Emcure Pharmaceuticals, India), glucometer (Accu-Check active; Roche Diagnostic India Pvt. Ltd), automated hematology analyzer (BC-5000; ASPEN Diagnostics), spectrophotometer (Shimadzu UV-1800), mild anesthesia, EDTA and all other reagents used were of analytical graded.

Plant Specimen Collection and Authentication

The fresh leaves of *M. dioica* Roxb. were collected from the RKDF University Campus, Bhopal, (M.P.) India. Plants selected for the research study were authenticated at the Department of Botany, Janata PG College, APS University, Rewa, M.P., India. Herbarium specimens were prepared and deposited with voucher specimen no. JC/B/PAN/483.

Preparation of Plant Extract

The extract was prepared using coarsely powdered leaves with 95% ethanol using a soxhlet apparatus. The ethanolic extract obtained was evaporated using a vacuum evaporator at reduced pressure and temperature to get the concentrate.[13] The crude extract obtained was stored in desiccators for use in research studies.

Experimental Animals

All animal experiments were performed in accordance with the ethical guidelines suggested by the Institutional Animal Ethics Committee (IAEC) at Vedica College of B. Pharmacy, RKDF University, Bhopal MP. The animals were used with permission number IAEC/VCP/2019/001/6. Adult Wistar male albino rats weighing 150 to 200 g were used for the *in-vivo* anti-diabetic study. The animals were housed in clean polypropylene cages and maintained in a well-ventilated, temperature-controlled animal house with a constant 12-hours light/dark schedule. The animals were fed standard rat-pelleted diet, and clean drinking water was made available ad libitum.

Experimental Design for Oral Glucose Tolerance Test

An oral glucose tolerance test was performed using normal rats. Overnight fasted rats were separated into four groups. All the animal groups were administered glucose (2 g/kg b.w.) orally.[14] Animals in group I was given normal saline (0.9% w/v NaCl). Groups III and IV were treated orally with ethanolic extracts of *Momordica dioica* leaves at a dose of 200 and 400 mg/kg b.w. Group II was treated using the standard drug glibenclamide at 5 mg/kg b.w.[15] For glucose level estimation, blood samples were collected just after glucose administration at 0, 30, 60, 120, and 180 minutes by pricking the tail of each animal using Accu-chek glucometer.

Experimental Design for Anti-diabetic Activity

The animals had fasted overnight and diabetes was induced by a single intraperitoneal injection of freshly prepared STZ (60 mg/kg b.w.) in 0.1 M citrate buffer-pH 4.5.[16] After 72 hours, STZ-induced fasted rats with blood glucose levels greater than 250 mg/dL were considered diabetic and used for further study. The animals had free access to a 5% glucose solution overnight to overcome the drug-induced hypoglycemia.

In this study, overnight fasted experimental rats were divided into five groups of six rats each to determine the anti-diabetic activity of ethanolic extracts of *M. dioica*. The diabetic groups of animals were administered saline, a standard drug (glibenclamide), and plant extracts for 28 days. The fasting blood glucose levels were estimated on the 0^{th}, 7^{th}, 14^{th}, 21^{st}, and 28^{th} days from the tail pricking of each animal. The rats were divided into groups comprising six animals each, as follows:

Grouping of Animals

Group I: Normal control	Normal saline
Group II: Diabetic control and normal saline	Streptozotocin 60 mg/kg

Table 1: Effect of *M. dioica* leaves extract on oral glucose tolerance test in normal rats.

Groups	*Blood glucose level (mg/dL)*				
	0 min	*30 mins*	*60 mins*	*120 mins*	*180 mins*
Normal Control	81.34 ± 1.37	150.67 ± 3.99	152.17 ± 2.64	144.5 ± 4.14	102.38 ± 3.14
Positive Control	82.17 ± 2.56	142.8 ± 3.31	140.33 ± 1.75	109.66 ± 4.32**	88.83 ± 3.25**
MDL200	80.25 ± 1.87	140.84 ± 3.98	144.50 ± 3.4	115.16 ± 3.54*	94.16 ± 2.13**
MDL400	83.42 ± 2.58	145.16 ± 4.62	141.16 ± 1.94	112.34 ± 3.44*	90.17 ± 2.92**

Values are given as mean ± SD (n = 6), values are statistically significant at *$p < 0.05$, more significant at **$p < 0.01$ vs. control

Table 2: Effect of *M. dioica* leaves extract on the fasting blood glucose levels in diabetic rats.

Fasting blood glucose levels (mg/dL)					
Animal Groups	*0 Day*	*7 Day*	*14 Day*	*21 Day*	*28 Day*
Normal Control	81.34 ± 1.37	80.66 ± 2.25	84.16 ± 2.48	82.5 ± 3.27	83.67 ± 2.87
Diabetic Control	257.17 ± 4.70	251.83 ± 7.81	255.50 ± 6.80	244.34 ± 4.76	256.16 ± 4.66
Positive Control	255.10 ± 5.06	209.84 ± 4.99	161.42 ± 3.62*	129.67 ± 4.18*	91.5 ± 2.88**
MDL 200	249.33 ± 4.22	211.5 ± 5.31	164.11 ± 3.16*	133.18 ± 2.92*	98.41 ± 2.59**
MDL 400	256.66 ± 5.93	215.46 ± 3.31	158.34 ± 2.87*	131.16 ± 2.31*	93.5 ± 4.32**

Values are given as mean ± SD (n = 6), values are statistically significant at *$p < 0.05$, more significant at **$p < 0.01$ vs. control

Table 3: Effect of *M. dioica* leaves extract on body weight of diabetic rats

Animal Groups	*Animals Body Weight (g)*				
	0 Day	*7 Day*	*14 Day*	*21 Day*	*28 Day*
Normal Control	176.83 ± 2.73	180.72 ± 3.91	181.5 ± 4.72	180.66 ± 4.03	182.5 ± 3.78
Diabetic control	175.16 ± 3.98	162.83 ± 2.85	153.61 ± 3.2	147.16 ± 3.71	141.91 ± 3.55
Positive control	170.43 ± 2.51	175.16 ± 2.13**	177.96 ± 3.95**	181.5 ± 6.83**	186.51 ± 2.05
MDL200	168.66 ± 4.71	171.83 ± 7.78**	174.26 ± 4.23**	178.16 ± 7.96**	180.21. ± 3.43**
MDL400	170.56 ± 3.35	175.96 ± 4.96**	179.8 ± 5.54**	182.5 ± 8.26**	184.75 ± 3.17**

Values are given as mean ± SD (n = 6), values are statistically significant at *$p < 0.05$, more significant at **$p < 0.01$ vs. control

Table 4: Effect of *M. dioica* leaves extract on lipid profiles in diabetic rats

Animal Groups	*Serum lipid level on 28th Day of the study*				
	Triglyceride (mg/dL)	*Total Cholesterol (mg/dL)*	*HDL-C (mg/dL)*	*LDL-C (mg/dL)*	*VLDL-C (mg/dL)*
Normal Control	92.83 ± 1.47	79.66 ± 1.63	48.31 ± 1.06	44.33 ± 2.5	15.26 ± 1.01
Diabetic Control	167.16 ± 3.18	133.86 ± 1.55	26.83 ± 1.47	101.16 ± 2.13	36.34 ± 0.81
Positive Control	96.25 ± 0.75**	81.36 ± 1.60**	45.236 ± 1.21**	49.25 ± 1.93**	17.1 ± 0.78**
MDL 200	103.08 ± 1.96*	85.34 ± 1.36**	41.68 ± 1.31**	55.16 ± 1.72**	19.48 ± 1.39*
MDL 400	98.5 ± 1.51**	82.33 ± 1.21**	44.16 ± 1.48**	51.26 ± 1.69**	16.85 ± 0.67**

Values are given as mean ± SD (n=6), values are statistically significant at *$p < 0.05$, more significant at **$p < 0.01$ vs. control

Group III: Positive control Diabetic rats treated with glibenclamide at 5 mg/kg b.w.
Group IV: MDL 200 Diabetic rats were given an ethanolic extract of MDL 200 mg/kg body weight.
Group V: MDL 400 Diabetic rats were given an ethanolic extract of MDL 400 mg/kg body weight.

Evaluation of OGTT and Anti-diabetic Activities

The OGTT using normal rats was performed to evaluate the effects of *M. dioica* leaves ethanolic extracts MDL 200 and MDL 400 mg/kg. Blood samples were analyzed in the OGTT at 0, 30, 60, 120, and 180 minutes.[17] Anti-diabetic effects of MDL 200 and 400 were studied using STZ-induced diabetes. Fasting blood glucose level was determined on days 0, 7, 14, 21, and 28 of the study after once-daily administration of test extracts and standard drugs.

Biochemical Parameters

At the end of the experimental period, i.e., after 28 days, rats were sacrificed by cervical dislocation under mild anesthesia. Blood samples were collected through the arterial jugular with EDTA. Plasma and serum were separated by centrifugation at 3000 rpm for 10 minutes at 30°C and analyzed for diabetes-related biochemical parameters such as lipid profile,[18] glycosylated hemoglobin (HbA1c), serum urea, and creatinine.

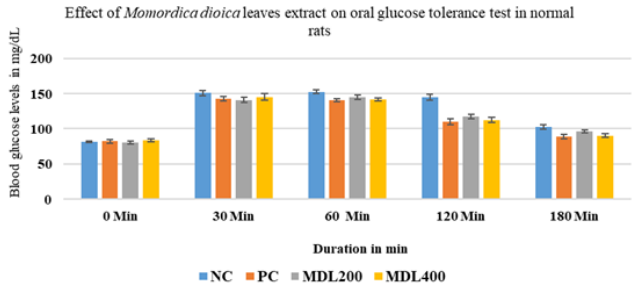

Fig. 1: Effect of *M. dioica* leaves extract on oral glucose tolerance test in normal rats

Table 5: Effect of *M. dioica* leaves extract on glycosylated hemoglobin levels in diabetic rats

Animal Groups	*Glycosylated hemoglobin (HbA1c %)*
Normal Control	5.65 ± 0.29
Diabetic Control	11.65 ± 0.55
Positive Control	5.90 ± 0.24**
MDL 200	5.95 ± 0.21*
MDL 400	5.80 ± 0.34**

Values are given as mean ± SD (n = 6), Values are statistically significant at *$p < 0.05$, more significant at **$p < 0.01$ Vs control

Table 6: Effect of *M. dioica* leaves extract on serum creatinine and urea levels in diabetic rats

Animal Groups	*Creatinine (mg/dL)*	*Urea (mg/dL)*
Normal Control	0.73 ± 0.012	15.74 ± 0.91
Diabetic Control	1.01 ± 0.048	27.20 ± 0.014
Positive Control	0.77 ± 0.021**	19.68 ± 0.062**
MDL 200	0.86 ± 0.018*	20.89 ± 0.06**
MDL 400	0.83 ± 0.027**	19.26 ± 0.057**

Values are given as mean ± SD (n=6), Values are statistically significant at *$p < 0.05$, more significant at **$p < 0.01$ Vs control

Serum was stored in the refrigerator at 4–8°C before analysis.[19,20] The pancreas of the experimental rats was removed after the autopsy of rats for histopathological studies, and a portion of each was stored in formalin for performing the antioxidant assays.[21]

Antioxidant Assay

An antioxidant assay was performed by measuring, superoxide dismutase (SOD), catalase activities (CAT), and

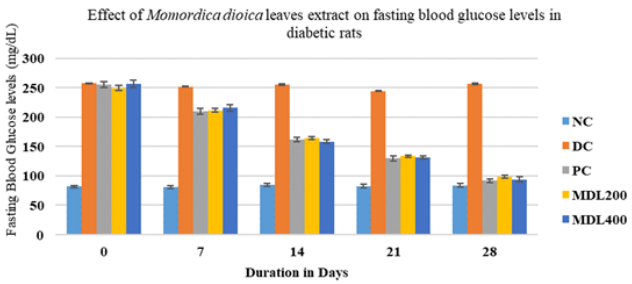

Fig. 2: Effect of *M. dioica* leaves extract on fasting blood glucose levels in diabetic rats

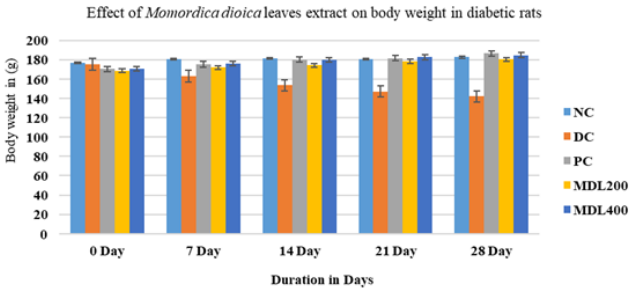

Fig. 3: Effect of *M. dioica* leaves extract on body weight in diabetic rats

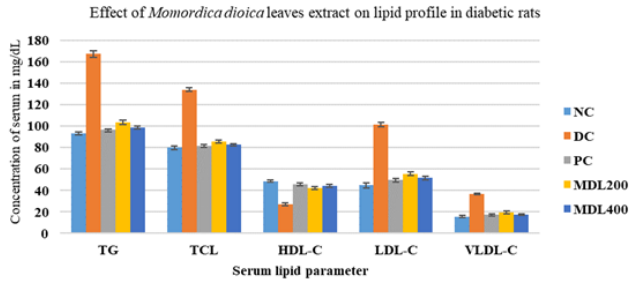

Fig. 4: Effect of *M. dioica* leaves extract on the lipid profiles in diabetic rats

reduced glutathione (GSH) levels in the pancreatic tissues of normal, diabetic control, and MDL-treated rats.[22]

Histopathological Study

Histopathological studies of the pancreas isolated from the sacrificed rats were performed. The tissues were washed with normal saline immediately and fixed in 10% formalin for 24 hours. Tissues were dehydrated with alcohol, embedded in paraffin, and then cut into 4–5 m-thick

Table 7: Effect of M. dioica leaves extracts on antioxidant levels in diabetic rats

Animal groups	*SOD (µg/mg tissue)*	*CAT (µmol/mg tissue)*	*GSH (µmol/mg tissue)*
Normal Control	27.64 ± 1.52	51.12 ± 2.42	39.81 ± 2.37
Diabetic Control	13.58 ± 1.25	19.66 ± 1.15	11.05 ± 1.05
Positive Control	25.82 ± 1.32**	48.63 ± 1.30**	38.64 ± 1.78**
MDL 200	22.41 ± 1.62*	45.76 ± 1.84*	33.89 ± 1.18*
MDL 400	25.71 ± 1.17**	49.53 ± 1.63**	37.28 ± 1.02**

Values are given as mean ± SD (n = 6), values are statistically significant at *$p < 0.05$, more significant at **$p < 0.01$ vs. control

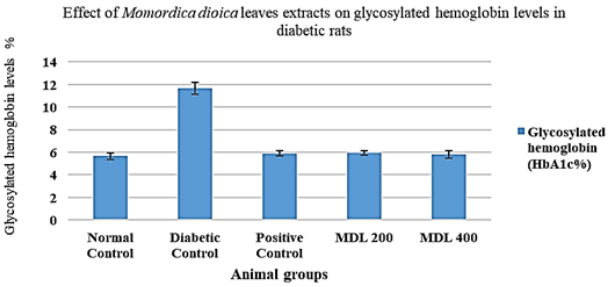

Fig. 5: Effect of *M. dioica* leaves extract on glycosylated hemoglobin levels in diabetic rats.

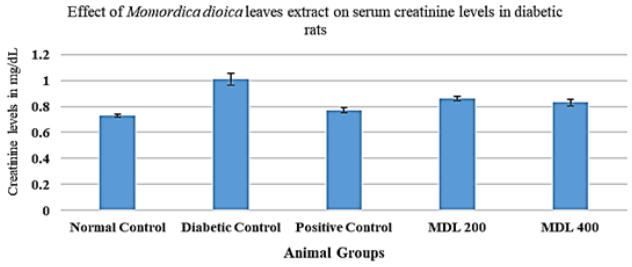

Fig. 6: Effect of *M. dioica* leaves extract on serum creatinine levels in diabetic rats.

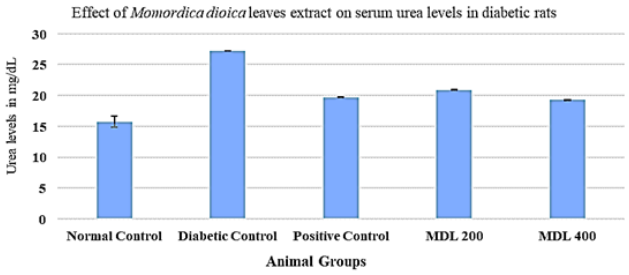

Fig. 7: Effect of *M. dioica* leaves extract on serum urea in diabetic rats.

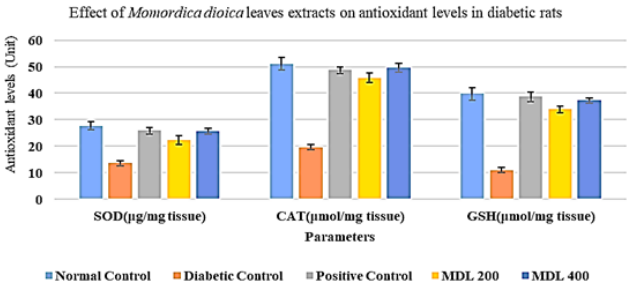

Fig.8: Effect of *M. dioica* leaves extracts on antioxidant levels in diabetic rats.

sections and stained with hematoxylin-eosin dye. Finally, photomicroscopic observations were performed.[22]

Statistical Analysis

All the results were expressed as mean ± SD (n = 6) in each experimental group. GraphPad Prism version 5.0 was used to analyse the data statistically. The data was evaluated using a one-way analysis of variance (ANOVA) followed by Dunnett's test. p-values < 0.05 were considered statistically significant, p< 0.01 as very significant.

Results

Oral Glucose Tolerance Test

The OGTT was performed on normal glycemic rats. After glucose administration, the blood glucose levels increased in the first 30 min in all four groups. It gradually started decreasing after 120 minutes and got normalized at 180 minutes, which has been shown in Table 1 and illustrated in Fig. 1. In the OGTT study, it was also revealed that oral administration of MDL 200 and 400 mg/kg both significantly (p < 0.01) reduced the blood glucose concentrations by 33.15 and 37.88% to the normal as a positive control (37.82%).

Anti-diabetic Activity

The study discovered that administering MDL doses of 200 and 400 mg/kg for 28 days reduced fasting blood glucose levels, which were significantly elevated in STZ-induced diabetic rats by 206.82% when compared to the normal control. The MDL significantly (p < 0.05) reduced the blood glucose level by 60.53% and 63.57% toward normal as compared to the diabetic control group. Whereas the positive control group showed a 64.13% reduction, which has been depicted in Table 2 and illustrated by Fig. 2.

Effect on the Body Weight of Animals

All animals ingested normal amounts of food and water during the study period. Slightly reduced body weight due to STZ-induced diabetes, significantly reverted to normal weight in all animals except the diabetic control group, as summarized in Table 3 and illustrated by Fig. 3. During the 28th day of the diabetes study, the diabetic control group's body weight decreased by 18.98%, but this was not observed with MDL treatment.

Estimation of Lipid Profile

In STZ-induced diabetic rats, there was a significant increase in triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) cholesterol, i.e., by 80.07, 68.04, 128.20, and 138.13%, respectively, and a significant decrease in high-density lipoprotein (HDL) cholesterol in serum, 44.47% compared with normal control, was observed. Thus, the ethanolic extract used in the study significantly reverted the disturbed lipid profile parameters. As depicted in Table 4 and illustrated in Fig. 4.

Estimation of Glycosylated Hemoglobin

In STZ-induced diabetic rats, there was a significant increase in HbA1c by 106.19% compared with the normal control. On treatment with ethanolic extract, MDL 200 and 400 reverted the elevated HbA1c profile by 48.07

and 50.21%, compared to diabetic control, which was as significant as a positive control at 46.79%. Results have been depicted in Table 5 and illustrated by Fig. 5.

Estimation of Creatinine and Urea

In STZ-induced diabetic rats, there was a significant increase in creatinine and urea by 38.35 and 72.80% compared with the normal control. Whereas ethanolic extract of MDL 200 and 400, reverted the elevated creatinine by 14.86 and 17.83%, and urea by 23.19 and 29.20%, compared to diabetic control, which was as significant as a positive control at 23.76 and 27.64%, respectively. Results have been depicted in Table 6 and illustrated in Figs. 6 and 7.

Antioxidant Assay

SOD, CAT, and GSH levels in STZ-induced diabetic rats were reduced by 50.86, 61.55, and 72.24%, respectively, when compared to normal controls. Whereas ethanolic extract MDL 200 and 400 reverted the reduced SOD, CAT, and GSH significantly compared to diabetic control and were as significant as a positive control. SOD level improved by 65.02 and 89.32%, CAT improved by 132.75 and 151.94%, whereas GSH improved by 206.69 and 237.37%. Results have been depicted in Table 7 and illustrated in Fig. 8.

Histopathological Studies

Pancreatic histopathological observations revealed that MDL-treated groups exhibited marked improvement in the density of pancreatic β-cell activity in a dose-dependent manner as compared to diabetic rats. In diabetic rats, the pancreas showed atrophy of islet cells with inflammatory edema, necrosis, fibrotic changes, and shrinkage. These alterations in the histology were revered to near normal after the treatment with MDL 200, 400 and standard treatment.

Discussion

The oral glucose tolerance test (OGTT) is widely used to evaluate apparent insulin release and insulin resistance in various clinical settings.[23] In the oral glucose tolerance test, glucose was given orally after administration of various test extracts and the standard drug, 2 g/kg b.w., and blood glucose levels were estimated at various time intervals. The results revealed that the drugs significantly improved the oral glucose tolerance in rats and exhibited potent anti-diabetic activity, which could be due to the accumulation of their islet cells that reverted to normal after treatment with MDL extract. The result of the accumulation of their common active constituents or the synergic action of different compounds present.

STZ elevated blood sugar levels significantly, and diabetes was developed in experimental rats. After 28 days of treatment with MDL 200 and 400 in diabetic rats, blood glucose levels significantly reduced to near normal as the standard drug. Anti-diabetic effect of the extract might have been achieved by different possible mechanisms including inhibiting starch digestion, decreasing glucose absorption from the intestine, enhancing insulin secretion from β-cells by stimulating the damaged or destructed β-cells, inhibiting glucose formation in the bloodstream, and suppressing the transport of glucose.[24]

Indicated body weight loss due to muscle wasting was observed in diabetic rats compared to normal rats. This suggested loss of body weight may be due to excessive breakdown of tissue protein. Treatment with MDL stopped the progression and reversed the breakdown of tissue protein, thus improving body weight to a certain extent, indicating that control over muscle wasting resulted from glycemic control.

Diabetes is often associated with dyslipidemia, the main risk factor for cardiovascular diseases.[25] Therefore, serum triglycerides and cholesterol levels are usually elevated in diabetic patients. In the study, an increase in the concentration of cholesterol, triglycerides, LDL, and a decrease in HDL in STZ diabetic rats was observed. Chronic administration of MDL extracts normalizes the serum lipid profile, i.e., secondary to the diabetic state. Diabetes-induced hyper-lipidaemia is attributable to excess fat mobilization from adipose due to the underutilization of glucose. The regression of the diabetic state due to chronic administration of MDL extract increased glucose utilization, thereby depressing fat mobilization.[26]

In STZ-induced diabetic rats, a significant elevated level of HbA1c has been identified as a significant risk factor for cardiovascular diseases and stroke in subjects who may have diabetes.[27] If HbA1c is uncontrolled, sugar flow in the blood is high and might affect the kidneys. On treatment with MDL 200 and 400, HbA1c levels decreased to near normal values. This might have improved the plasma insulin level and helped to control the blood glucose level and utilization.

STZ has inherent nephrotoxic potential, hence it showed definite signs of nephrotoxicity and marked renal dysfunction as compared to the normal control group. This was evidenced by elevations of the serum urea and creatinine levels. However, MDL treatment for 28 days resulted in the reversal of altered elevation.[28]

Studies have shown that increased urea and creatinine concentrations were due to excessive lipolysis in severe DM, leading to ketosis and acidosis. By acidifying urine and removing metabolic wastes such as urea and creatinine, the kidney maintains the optimum chemical composition of body fluid. But in the case of renal function impairments or diseases, the concentration of these metabolites rises in the blood.[20] Treatment with MDL for 28 days on diabetic rats normalized the elevated level.

The elevated blood glucose level in diabetes facilitates free radical's production and thus depletes the natural antioxidants.[29] SOD, CAT, and GSH are important enzymes that scavenge free radicals and protect the cells against oxidative stress injury.[30]

In this study, decreased levels of SOD, CAT, and GSH were observed in diabetic rats, indicating a high level of oxidative stress. Administration of MDL significantly improved the levels of SOD, CAT, and GSH. This activity of the MDL might be correlated with the presence of supporting phytochemicals, such as flavonoids and phenols, that can scavenge free radicals.[31] Furthermore, the reversal of antioxidant enzyme concentrations in the diabetic rats treated with the MDL might have regenerated pancreatic β-cells that might have contributed to the anti-diabetic activity of the MDL extracts.[32]

A study of the pancreas in STZ-induced diabetic rats has shown gradual loss of β-cell, its function, and mass has been reported to lead to inhibition of insulin synthesis and hence an increase in blood glucose. The study found that preventing the loss of beta-cell function and mass and stabilising and/or regenerating them improves insulin synthesis and thus maintains blood glucose levels.[33]

Histopathology study of the pancreas showed that STZ induced necrosis, fibrotic changes, severely damaged β-cells, and caused lesions in the pancreas, which in turn caused loss of β -cell function and mass. After treatment with MDL, all the lesions and histopathological changes in the pancreas were significantly restored and were found to be comparatively better than those of standard glibenclamide treatment.

Conclusion

Ethanolic extract of *M. dioica* leaves possesses potent anti-diabetic activity, potentially improving body weight and associated disturbed biochemical parameters. It also significantly showed antioxidant activity and thus has the potential to improve diabetes-induced nephropathy. The study also validated the claim of the use of this plant in the management of diabetes mellitus as a folklore medicine. The result might be due to the presence of phenolic compounds, flavonoids, and saponins in the medicinal plant extract.

Acknowledgement

The authors are greatly thankful to the research facilities provided by RKDF University, Bhopal MP-462033, India.

REFERENCES

1. Govindappa M. A Review on Role of Plant(s) Extracts and its Phytochemicals for the Management of Diabetes. J Diabetes Metab. 2015; 6(7):565.
2. Patil R, Patil R, Ahirwar B, Ahirwar D. Current Status of Indian Medicinal Plants with Antidiabetic Potential: a review. Asian Pac J Trop Biomed. 2011; 1(2): S291–S298.
3. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R; IDF Diabetes Atlas Committee. Global and Regional Diabetes Prevalence Estimates for 2019 and Projections for 2030 and 2045 results from the International Diabetes Federation Diabetes Atlas 9th edition. Diabetes Res Clin Pract. 2019; 157:107843.
4. Mathur C, Gupta RS. A Review on Medicinal plants of Rajasthan Having Antidiabetic Activity. Asian J Pharm Clin Res. 2018; 11(12):33-39.
5. Patel DK, Prasad SK, Kumar R, Hemelatha S. An overview on Anti-diabetic Medicinal Plants having Insulin Mimetic Property. Asian Pac J Trop Biomed. 2012; 2(4):320-330.
6. Sharma P, Singh R. Effect of Momordica dioica fruit Extract on Antioxidant status in Liver, Kidney, Pancreas, and Serum of Diabetic Rats. Pharmacog Res. 2014; 6(1):73-79.
7. Kirtikar KR, Basu BD. Indian Medicinal Plants. International Book Distributors Dehradun, 1999.
8. Bawara B, Dixit M, Chauhan NS, Dixit VK, Saraf DK. Phyto-pharmacology of Momordica dioica Roxb. ex Willd: A Review. Int J Phytomed. 2010; 2(1):1-9.
9. Jain A, Nahata A, Lodhi S, Singhai AK. Effects of Tephrosia purpurea and Momordica dioica on Streptozotocin-induced Diabetic Nephropathy in Rats. Biomed Prevent Nut. 2014;4(3):383–389.
10. Joshi N, Shah KW, Mujalde S. Phytochemical Screening of whole Plant Extract of Momordica dioica (Roxb.). Int J Creat Res Thoughts. 2018; 6(1):251-253.
11. Nagarani G, Abirami A, Siddhuraju P. A Comparative Study on Antioxidant Potentials, Inhibitory Activities against key Enzymes Related to Metabolic Syndrome, and Anti-inflammatory Activity of leaf Extract from Different Momordica species. Food Sci Human Wellness. 2014; 3(1):36-46.
12. Devendra NK, Vijaykumar BM, Subhash B, Seetharam YN. Phytochemical Profile and Antibacterial Properties of the Fruit and Leaf of the Momordica dioica (Roxb.) Willd. Pharmacologyonline. 2010; 3:207-211.
13. Jain A, Soni M, Deb L, Jain A, Rout SP, Gupta VB, Krishna KL. Antioxidant and Hepatoprotective Activity of Ethanolic and Aqueous Extracts of Momordica dioica Roxb., leaves. J Ethnopharmacol.2008; 115(1):61–66.
14. Barik R, Jain S, Qwatra D, Joshi A, Tripathi GS, Goyal R. Antidiabetic Activity of Aqueous Root Extract of Ichnocarpus frutescens in Streptozotocin-nicotinamide induced type-II Diabetes in rats. Indian J Pharmacol. 2008; 40(1):19–22.
15. Soni LK, Dobhal MP, Arya D, Bhagour K, Parasher P, Gupta RS. In vitro and in vivo Antidiabetic Activity of Isolated Fraction of Prosopis cineraria against Streptozotocin-induced Experimental Diabetes: A mechanistic study. Biomed Pharmacother. 2018; 108:1015-21.
16. Kadali SL DVRM, Das MC, Vijayaraghavan R, Kumar MV. Evaluation of Antidiabetic Activity of Aqueous and Ethanolic Extracts of Leaves of Chloroxylon swietenia in Streptozotocin (STZ) induced Diabetes in Albino Rats. Biomed Pharmacol J. 2017; 10(3):1347-1347.
17. Kumar P, Michael M. Antidiabetic, Antihyperlipidemic and Antioxidant Activities of a Polyherbal Formulation in type 2 Diabetic Rats. J Diabetes Metab. 2020; 12(2):1000866.
18. Friedewald WT, Levi RI, Fredrickson DS. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. Clin Chem. 1972; 18(6):499-502.
19. De Tata V, Novelli M, Bombara M, Masiello P, Cappuccio A, Innocenti B, Bergamini, E. Determination of Glycated Hemoglobins in the rat: Comparison Between two Different Chromatographic Methods and Application in Experimental Diabetology. Res Exp Med. 1996; 196(1):9-16.
20. Gupta V and Kori ML. Assessment of Hepato And Nephroprotective Potential of Polyherbal Combinations Against STZ-induced Diabetic Liver and Kidney Complications in Wistar Rats. Ann Phytomed. 2022; 11(1):311-319.
21. Chakrabarti R, Vikramadithyan RK, Mullangi R, Sharma VM, Jagadheshan H, Rao YN, Sairam P, Rajagopalan R. Antidiabetic and Hypolipidemic Activity of Helicteres isora in Animal Models. J Ethno Pharmacol. 2002; 81(3):343-349.
22. Sharma N and Garg V. Antidiabetic and Antioxidant Potential of Ethanolic Extract of Butea Monosperma Leaves in Alloxan-induced Diabetic Mice. Indian J Biochem Biophys. 2009; 46(1):99-105.

23. Stuvoll M, Jarvien HY, Mitrakou A, Haeften TV, Pimenta W, Renn W. Use the Oral Glucose Tolerance Test to Assess Insulin Release and Insulin Sensitivity. Diabetes care. 2000; 23(3):295-301.
24. Kamtekar S, Keer V. Management of Diabetes: A review. Res J Pharm Tech. 2014; 7(9):1065-1072.
25. Kannel WB. Lipids, Diabetes, and Coronary Heart Disease: Insights from The Framingham Study. Am Heart J. 1985; 110:1100-1107.
26. Patil RN, Patil RY, Ahirwar B, Ahirwar D. Evaluation of Antidiabetic and Related Actions of Some Indian Medicinal Plants in Diabetic Rats. Asian Pac J Trop Biomed. 2011; 4(1):20-23.
27. Martin-Timon I, Sevillano-Collantes C, Segura-Galindo A, Del Canizo-Gomez FJ. Type 2 Diabetes and Cardiovascular Disease: Have all Risk Factors the Same Strength? World J Diabetes. 2014; 5(4):444-470.
28. Tang G, Li S, Zhang C, Chen H, Wang N, Feng Y. Clinical Efficacies, Underlying Mechanisms and Molecular Targets of Chinese Medicines for Diabetic Nephropathy Treatment and Management. Acta Pharmaceutica Sinica. 2021; 11(9): 2749-2767.
29. Mehta JL, Rasouli N, Sinha AK, Molavi B. Oxidative Stress in Diabetes: A Mechanistic Overview of its Effects on Atherogenesis and Myocardial Dysfunction. Int J Biochem Cell Biol. 2006; 38(5-6):794-803.
30. Kim JO, Kim KS, Lee GD, Kwon JH. Antihyperglycemic and Antioxidative Effects of New Herbal Formula in Streptozotocin-induced Diabetic Rats. J Med Food. 2009; 12(4):728-735.
31. Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoid Antioxidants: Chemistry, Metabolism and Structure-activity Relationships. The J Nutr Biochem. 2002; 13(10):572-584.
32. Hosseini A, Shafiee-Nick R, Ghorbani A. Pancreatic Beta Cell Protection/regeneration with Phytotherapy. Braz J Pharm Sci. 2015; 51(1):1-16.
33. Ramu R, Shirahatti PS, N Swamy S, Zameer F, Dhananjaya BL, Prasad MN. Assessment of in vivo Antidiabetic Properties of Umbelliferone and Lupeol Constituents of Banana (Musa sp. var. Nanjangud Rasa Bale) Flower in Hyperglycaemic Rodent Model. Plos One. 2016; 11(3):0151135.

HOW TO CITE THIS ARTICLE: Adlak P, Sagar R, Kori ML. Ethanolic Extract of *Momordica dioic*a Roxb. Leaves Show Potent Anti-diabetic Activity on Experimental Wistar Albino Rats. Int. J. Pharm. Sci. Drug Res. 2022;14(5):631-638. **DOI:** 10.25004/IJPSDR.2022.140518