Journal or Innovative Development in Pharmaceutical and Technical Science (JIDPTS)
Volume:9, Issue:11, Nov:2026

(J I D P T S)
ISSN(O):2581-6934

PHARMACOLOGICAL EVALUATION OF ANTIDIABETIC ACTIVITY OF ETHANOLIC EXTRACT OF MOMORDICA FOETIDA IN STREPTOZOTOCIN-INDUCED DIABETES IN RATS

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Abstract: The present study evaluated the antidiabetic and antioxidant potential of the ethanolic extract of Momordica foetida in Streptozotocin (STZ)-induced diabetic Wistar rats. Diabetes was induced by a single intraperitoneal injection of STZ (45–55 mg/kg). After confirmation of hyperglycemia, animals were treated orally for 21 days with the plant extract at doses of 200 and 400 mg/kg. Metformin (5 mg/kg, p.o.) served as the standard drug. Biochemical evaluations included fasting blood glucose, lipid profile (TC, TG, HDL, LDL, VLDL), liver function enzymes (AST, ALT, ALP), kidney function markers (urea, creatinine), and pancreatic antioxidant parameters (SOD, CAT, GSH, MDA). Diabetic control rats showed significant hyperglycemia, dyslipidemia, elevated hepatic and renal markers, and increased oxidative stress with reduced antioxidant enzyme levels. Treatment with the ethanolic extract of Momordica foetida produced a dose-dependent reduction in blood glucose and lipid abnormalities, restored liver and kidney function markers, and significantly improved pancreatic antioxidant status by elevating SOD, CAT, and GSH while decreasing MDA levels. The higher dose (400 mg/kg) showed effects comparable to Metformin. The study concludes that Momordica foetida exhibits significant antidiabetic activity mediated through antihyperglycemic, antihyperlipidemic, hepatoprotective, reno protective, and antioxidant mechanisms, supporting its traditional use and potential for development as a natural antidiabetic agent.

Keywords: Momordica foetida, Streptozotocin, Diabetes mellitus, Metformin, Antidiabetic activity.

INTRODUCTION

The maintenance of water and electrolyte balance in the human body is a complex physiological process essential for survival. One of the most critical me chanisms involved in this homeostatic function is antidiuretic activity, which refers to the reduction of urine output through increased water reabsorption in the kidneys. This activity is primarily mediated by antidiuretic hormone (ADH), also known as vasopressin, a peptide hormone secreted by the posterior pituitary gland. It acts on specific receptors in the renal system to conserve water and regulate osmolality and blood pressure. Dysregulation of this activity can lead to several clinical conditions, including diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and various states of fluid imbalance associated with heart failure, liver cirrhosis, or renal disease [1]. Antidiuretic activity represents an essential area of pharmacological investigation, especially in the context of understanding renal physiology and developing therapeutic interventions for fluid and electrolyte disorders. The phenomenon is not only relevant in clinical endocrinology but

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also holds significant implications in nephrology, critical care, and sports medicine. In addition, recent studies have begun to explore the role of plant-derived compounds and herbal medicines in modulating antidiuretic activity, which may serve as alternative or complementary therapies to conventional synthetic drugs. Water balance in the human body is regulated by intricate signaling pathways involving the hypothalamus, posterior pituitary, and renal tubules. When plasma osmolality increases or blood volume decreases, osmoreceptors in the hypothalamus trigger the release of ADH into the bloodstream. Upon reaching the kidneys, ADH binds to vasopressin V2 receptors located on the basolateral surface of principal cells in the renal collecting ducts. This binding activates adenylate cyclase via G-protein coupled mechanisms, leading to an increase in cyclic adenosine monophosphate (cAMP) levels. As a result, protein kinase A (PKA) is activated, which promotes the insertion of aquaporin-2 water channels into the apical membrane of collecting duct cells [2]. Through these channels, water is reabsorbed from the filtrate back into the bloodstream, effectively reducing urine volume and concentrating the urine. In the absence or insufficient action of ADH, water reabsorption is impaired, leading to polyuria (excessive urination) and polydipsia (excessive thirst), as seen in diabetes insipidus. Conversely, inappropriate or excessive secretion of ADH, as in SIADH, can result in hyponatremia and water retention, which may have serious neurological consequences.

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These herbal agents may influence antidiuretic mechanisms either directly by interacting with ADH receptors or indirectly by modifying renal tubular function or systemic hormones. However, scientific validation through in vivo models, biochemical analysis, and clinical trials is essential to confirm their efficacy and safety [5].

MATERIALS AND METHODS

Collection and authentication of Plant material

The Momordica foetida, was selected for investigation and were procured from the nearest area of Ranga reddy district Hyderabad. The plant material was taxonomically identified and authenticated by Dr. Madhava Chetty, Head of Department, Botany, Sri Venkateshwara academia, Tirupathi, Andhra Pradesh.

Preparation of plant extract

The Momordica foetida was air dried in shade and extracted with methanol and in a ratio of 50:50 for methanol extract, using a Soxhlet extractor for 8 hrs at 55-600C. The supernatant was filtered through Whatman filter paper No.1 and concentrated under reduced pressure using vacuum at 44 ± 100C in a rotavapor (IKA ® RB 10 Rota Evaporator, India) The extract was stored at 220C in a seeded air tight container.

The percentage of extract yield was calculated by using the formula

$$\%\ of\ extract\ yield = \frac{weight\ in\ gm\ of\ extract\ obtained}{weight\ in\ gm\ of\ plant\ material\ taken} \times 100$$

Animals and Management

Wistar albino rats of both sexes measuring between 150 and 200 gm were used. The animals were picked up from the residence of the pets, from our institute. The pets were randomly put upon entry and assigned as bedding in polypropylene tanks with paddy husk to treatment groups. Animals were housed at a temperature of 24±2oC and relative humidity of 30 to 70 %. A 12:12 light: day cycle was followed. All animals were allowed to free access to water and fed with standard commercial pelleted rat chaw Jeeva life sciences The Institutional Animal Ethics Committee CCSEA) studied all the laboratory processes and protocols used in this research and complied with the institutional ethical standards.

Acute Toxicity Study

The acute toxicity study is use to establish the therapeutic index, i.e. the ratio between the pharmacologically effective dose and lethal dose on the same strain and species (LD50/ED50). Greater is the index; safer is the compound and vice versa. The acute toxicity study was done according to OECD (Organization of Economic Co-operation and Development) guidelines 425- Fixed Dose Procedure (FDP).

Procedure:

The animals were divided into two groups and each group consisted of five rat. The defined or fixed dose level of aqueous and ethanolic extracts (2000 mg/kg) were given orally to identify a dose producing evident toxicity. The animals were observed continuously for 2 hours for behavioral, neurological and autonomic profiles. The toxicity signs were observed after 24 hours till fourteen days for any lethality or death. Hence in our studies we selected 1/4th and 1/8th of the highest dose.

Preparation of Doses

Doses equivalent to 500 mg and 250 mg of the crude drug per kilogram body weight were calculated, and suspended in 1% w/v tween 80 solutions for the experiment.

Oral Glucose Tolerance Test [6]

It is the test for the diagnosis of diabetes. It can be made on the basis of individual's response to the oral glucose load, commonly referred to as oral glucose tolerance test (OGTT). The response of standard oral test dose of glucose was determined. For this study normal rats were selected.

Induction of Diabetes [7]

Diabetes was induced106 by a single intraperitoneal injection of 60 mg/kg Streptozotocin 120 mg/kg, i.p, 15 min afterwards. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h and then on day 7 after injection. The threshold value of fasting plasma glucose to diagnose diabetes was taken as >126 mg/dl93. Only those rats that were found to have permanent NIDDM were used for the study. The diabetic rats after confirmation of stable hyperglycemia, were divided into 5 different groups of 6 rats each. That day was considered as the 0th day. Drug and doses were administered as mentioned.

Experimental grouping

Group I	Normal control	0.5% CMC (vehicle)	1 mL/kg, p.o.
Group II	Diabetic control	STZ only + vehicle	STZ 45–55 mg/kg, i.p.; CMC p.o.
Group III	Standard drug	STZ + Metformin	5 mg/kg, p.o.
Group IV	Test low dose	STZ + Ethanolic extract	200 mg/kg, p.o.
Group V	Test high dose	STZ + Ethanolic extract	400 mg/kg, p.o.

Preparation of streptozotocin solution [8] : streptozotocin solution was freshly prepared by dissolving 480 mg of streptozotocin in 8 ml of 0.9 % NaCl solution, and the volume of the solution was made up to 10 ml with the same solution.

Analysis of serum Lipid Profile and Total Protein

Total cholesterol (TC), triglycerides (TG), high-density lipoprotein, cholesterol (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein cholesterol (VLDL) blood levels were evaluated according to conventional techniques. Total protein in the homogeneous tissue was measured by Lowry et al. (1951) technique114 using bovine serum albumin as a standard. Similarly, blood urea assessment115 and serum creatinine analysis116 were done by standard technique and were reported.

Total cholesterol [9]

Total cholesterol in serum was determined by a colorimetric method. The assay principle is based on enzymatic hydrolysis and oxidation of cholesterol and the indicator compound, quinonimine is formed from hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase. The reagents consisted of 4-aminoantipyrine (0.03 mmol/l), phenol (6 mmol/l), peroxidase (≥0.5 U/ml), cholesterol esterase (> 0.15 U/ml), cholesterol oxidase (> 0.1 U/ml) and pipes buffer (80 mmol/L pH 6.8). The serum sample (10 µl) was mixed with 1 ml of reagent, incubated at 37oC for 5 min, and absorbance measured at 500 nm against the reagent blank 117. The cholesterol standard was 5.17mmol/l (200 mg/dl). The concentration of total cholesterol in the sample was calculated by Total cholesterol=(ΔA sample)/(Δ A standard)×concentration of standard

Triglycerols

Serum triacylglycerol's (TG) were determined by a colorimetric method. The assay principle is based on the enzymatic hydrolysis of TG with lipases and the indicator is a quinonimine formed from hydrogen-peroxide, 4- amino phenazone and 4-chlorophenol under the catalytic activity of peroxidase118. The enzyme reagent consisted of 4-aminophenazone (0.5 mmol/l), ATP (1.0 m.mol/l), lipases (≥150 U/ml), glycerol-kinase (≥0.4 U/ml), glycerol-3-phosphate oxidase (≥1.5 U/ml), peroxidase (≥0.5 u/ml). The serum sample (10 µl) was mixed with 1000 µl of enzyme reagent, incubated at 37oC for 5 min and absorbance measured at 500 nm against the reagent blank. The TG standard was 200 mg/dl (2.29mmol/l). The concentration of TG in the serum was calculated by Total triacylglycerol =(ΔA sample)/(Δ A standard)×concentration of standard

HDL Cholesterol [10]

Serum HDL cholesterol was determined by a colorimetric method. The assay principle is based on the following: the low-density lipoproteins (LDL and VLDL) and chylomicron fraction is precipitated quantitatively by the addition of phophotungstic acid in the presence of magnesium ions. After centrifugation, the cholesterol concentration in the HDL fraction, which remains in the supernatant, is determined. The precipitation reagents consisted of phosphotungstic acid (0.55mmol/l) and magnesium chloride (25 mmol/l). The serum sample (200 µl) was mixed with 500 µl of precipitation reagent and centrifuged at 4000 rpm for 10 min. The supernatant (100 µl) was mixed with reagent, incubated at 37oC for 5 min and absorbance measured at 500 nm against the reagent blank119. The cholesterol standard was 200 mg/dL (5.17 mmol/l). The concentration of cholesterol in the supernatant was calculated by. HDL Cholesterol =(ΔA sample)/(Δ A standard)×concentration of standard

LDL & VLDL Cholesterol

Low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) was calculated according to Friedwald formula120.

LDL = TC – HDL – VLDL,

VLDL cholesterol = Triglycerides / 5.

Estimation of Blood Urea

Estimation of blood urea nitrogen was performed according to method Natelson et al., 121 1951. Labeled three test-tubes as B, T and S. In to B, pipette, 0.02 ml water, into T, 0.02 ml blood and into S, 0.02 ml standard urea solution (40 mg urea in 100 ml of water). 0.1 ml of diacetyl monoxime solution and 5 ml of acid regent (Thiosemicarbazide) was added into all the test-tubes. Mixed and kept in a boiling water bath for 15 minutes. After cooling, the absorbance was read at 540 nm and concentration of urea in mg/dl was calculated.

Estimation of Serum Creatinine

The serum creatinine was estimated by method116 Slot, 1965. Labeled three test-tubes as B, T and S. into B, pipetted, 2 ml of water, into T, 2 ml serum and 4 ml of water, into S, 3 ml of water and 1 ml of creatinine standard (4mg/dl). 2 ml of ammonium sulphate and 2 ml of sodium tungstate was added in all the three test-tubes. Centrifuged and removed 3 ml of supernatant from each test tube. 1 ml of picric acid and distilled water was added to the supernatant of test tubes B, T and S. Absorbance was read at 520 nm and concentration of serum creatinine in mg/dl was calculated.

Statistical Analysis

The values were expressed as mean ± SEM. The statistical analysis was carried out by one way analysis of variance (ANOVA) followed by Dunnet's 't'- test. P values <0.05 were considered significant.

Results

Percentage of yield

$$\text{Percentage of yield} = \frac{\text{Weight of crude extract}}{\text{Weight of dried material}} \times 100$$

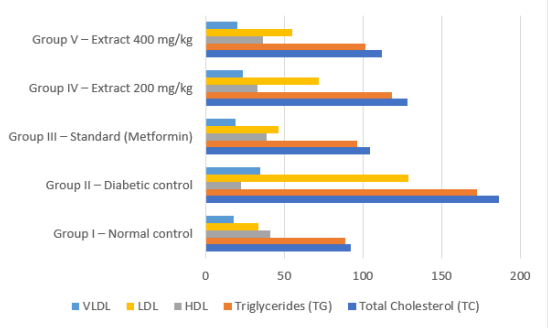
$$\text{Percentage of yield} = \frac{12g}{50g} \times 100 = 24\%$$

Lipid Profile Results (TC, TG, HDL, LDL, VLDL)

Model: STZ-induced diabetic Wistar rats treated with ethanolic extract of Momordica foetida after induction with Streptozotocin; standard drug Metformin. Duration: 21 days • n = 6/group

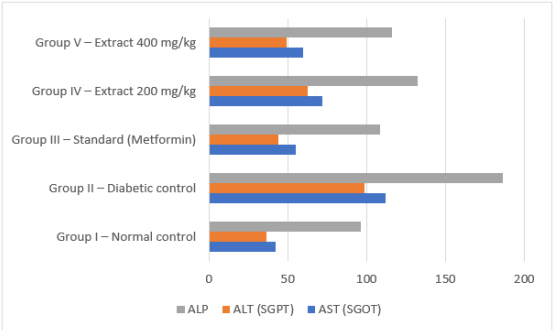
Values expressed as Mean ± SEM (mg/dL)

Group	Total Cholesterol (TC)	Triglycerides (TG)	HDL	LDL	VLDL
Group I – Normal control	92.4 ± 3.1	88.6 ± 2.8	41.2 ± 1.9	33.5 ± 2.1	17.7 ± 0.9
Group II – Diabetic control	186.3 ± 5.4	172.8 ± 4.9	22.6 ± 1.4	129.1 ± 3.8	34.6 ± 1.2
Group III – Standard (Metformin)	104.8 ± 3.6	96.2 ± 3.1	38.9 ± 1.7	46.7 ± 2.4	19.2 ± 1.0
Group IV – Extract 200 mg/kg	128.6 ± 4.2	118.4 ± 3.7	32.8 ± 1.6	71.9 ± 2.9	23.7 ± 1.1
Group V – Extract 400 mg/kg	112.3 ± 3.8	101.6 ± 3.3	36.7 ± 1.8	55.3 ± 2.6	20.3 ± 0.9



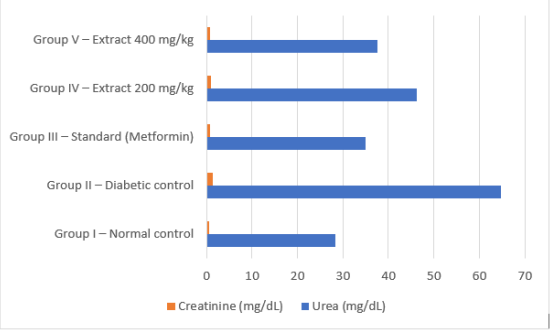
Liver Enzymes (AST, ALT, ALP)

Group	AST (SGOT)	ALT (SGPT)	ALP
Group I – Normal control	42.6 ± 2.1	36.8 ± 1.9	96.4 ± 3.2
Group II – Diabetic control	112.3 ± 4.8	98.7 ± 4.1	186.5 ± 5.6
Group III – Standard (Metformin)	54.9 ± 2.6	44.2 ± 2.3	108.7 ± 3.9
Group IV – Extract 200 mg/kg	71.8 ± 3.1	62.5 ± 2.8	132.4 ± 4.5
Group V – Extract 400 mg/kg	59.6 ± 2.7	49.3 ± 2.4	116.2 ± 4.1



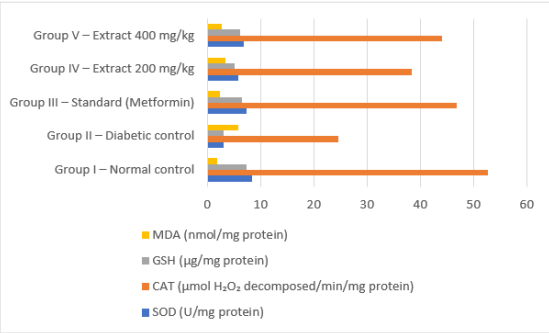
Kidney function markers (urea, creatinine)

Group	Urea (mg/dL)	Creatinine (mg/dL)
Group I – Normal control	28.4 ± 1.6	0.62 ± 0.04
Group II – Diabetic control	64.7 ± 2.9	1.48 ± 0.07
Group III – Standard (Metformin)	34.9 ± 1.8	0.78 ± 0.05
Group IV – Extract 200 mg/kg	46.2 ± 2.1	1.02 ± 0.06
Group V – Extract 400 mg/kg	37.6 ± 1.9	0.84 ± 0.05



Antioxidant Parameters in Pancreatic Tissue (SOD, CAT, GSH, MDA)

Group	SOD (U/mg protein)	CAT (µmol H_2O_2 decomposed/min/mg protein)	GSH (µg/mg protein)	MDA (nmol/mg protein)
Group I – Normal control	8.42 ± 0.36	52.8 ± 2.1	7.36 ± 0.28	1.92 ± 0.09
Group II – Diabetic control	3.15 ± 0.22	24.6 ± 1.4	3.02 ± 0.19	5.84 ± 0.21
Group III – Standard (Metformin)	7.36 ± 0.31	46.9 ± 1.8	6.58 ± 0.24	2.36 ± 0.11
Group IV – Extract 200 mg/kg	5.82 ± 0.27	38.4 ± 1.6	5.14 ± 0.22	3.48 ± 0.15
Group V – Extract 400 mg/kg	6.94 ± 0.29	44.1 ± 1.7	6.12 ± 0.23	2.71 ± 0.12



Discussion

Diabetes induced by Streptozotocin is characterized by pancreatic β-cell damage, persistent hyperglycemia, dyslipidemia, oxidative stress, and progressive hepatic and renal dysfunction. In the present study, ethanolic extract of Momordica foetida produced significant protection against these diabetes-associated alterations, comparable to the standard drug Metformin.

STZ administration markedly elevated serum glucose and produced classical diabetic dyslipidemia, evidenced by increased TC, TG, LDL, and VLDL with a reduction in HDL. Treatment with the extract corrected these abnormalities in a dose-dependent manner, with400 mg/kg approaching the Metformin group. This antihyperlipidemic effect may be attributed to improved insulin sensitivity and modulation of lipid metabolism, thereby reducing cardiovascular risk associated with diabetes. Hepatic marker enzymes (AST, ALT, ALP) were significantly elevated in diabetic control rats, indicating hepatocellular injury and altered membrane permeability due to oxidative stress. Administration of the extract significantly reduced these enzymes, suggesting hepatoprotective action. Restoration of liver enzymes toward normally indicates stabilization of hepatocyte membranes and improved metabolic function. Similarly, kidney function markers (urea and creatinine) were elevated in diabetic rats, reflecting renal impairment caused by prolonged hyperglycemia and oxidative damage. Extract treatment lowered these parameters, especially at 400 mg/kg, indicating renoprotective potential and improved glomerular function. Assessment of pancreatic antioxidant status revealed a severe decline in SOD, CAT, and GSH levels with a concomitant rise in MDA in diabetic control rats, confirming oxidative stress–mediated pancreatic damage. Treatment with the extract significantly restored antioxidant enzymes and reduced lipid peroxidation, nearly comparable to Metformin. This suggests that the antidiabetic effect of Momordica foetida is strongly linked to its antioxidant phytoconstituents (flavonoids, phenolics, triterpenoids), which protect β-cells from oxidative injury. the study demonstrates that ethanolic extract of Momordica foetida exerts multifaceted antidiabetic activity through glycemic control, correction of dyslipidemia, hepatic and renal protection, and enhancement of endogenous antioxidant defense in pancreatic tissue. The effects were dose dependent, with 400 mg/kg showing pronounced efficacy close to standard Metformin therapy, supporting its traditional use in diabetes management and its potential as a source of bioactive antidiabetic compounds.

Conclusion

The present study demonstrates that the ethanolic extract of Momordica foetida possesses significant antidiabetic potential in Streptozotocin-induced diabetic rats. Oral administration of the extract for 21 days produced a dose-dependent improvement in glycemic status, lipid profile, liver enzymes (AST, ALT, ALP), and kidney function markers (urea, creatinine). The extract also markedly restored pancreatic antioxidant defenses by increasing SOD, CAT, and GSH levels while reducing MDA, indicating protection against oxidative stress–mediated β-cell damage. The higher dose (400 mg/kg) showed effects comparable to the standard drug Metformin. that Momordica foetida exerts multidimensional antidiabetic activity through antihyperglycemic, antihyperlipidemic, hepatoprotective, Reno protective, and antioxidant mechanisms. These results scientifically validate its traditional use and indicate its promise as a potential source of natural antidiabetic agents for further phytochemical isolation and clinical exploration.

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