

Hypoglycemic and Hypolipidemic Effects of *Leonotis mollissima* Aqueous Leaf Extract in Type 2 Diabetic Rats

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Purpose: Type 2 diabetes is a global health challenge, prevalent in Uganda in about 3.6% of cases. Despite the availability of conventional treatments, there is a growing interest in natural remedies due to their potential efficacy and fewer side effects. This study evaluated *Leonotis mollissima* aqueous leaf extract for hypoglycemic and hypolipidemic effects in type 2 diabetic rats, given its traditional use and limited scientific validation.

Patients and Methods: Diabetes was induced in Wistar rats using a high-fat diet (60% fat; 40% carbohydrate, 15% protein, 0.5% cholesterol) and streptozotocin (35 mg/kg). Rats received *Leonotis mollissima* extract (250, 500, 1000 mg/kg) or glimepiride (5 mg/kg; sulfonylurea insulin secretagogue) for 28 days. Fasting blood glucose, oral glucose tolerance, glycated hemoglobin, lipid profiles, and pancreatic histology were assessed.

Results: *Leonotis mollissima* (1000 mg/kg) significantly reduced fasting blood glucose levels ($p = 0.0172$ vs negative control group), improved glucose tolerance ($p < 0.0001$), and lowered glycated haemoglobin levels in a dose-dependent manner. *Leonotis mollissima* (1000 mg/kg) also improved lipid profiles by reducing total cholesterol ($p = 0.0016$ vs negative control), and low-density lipoprotein-cholesterol levels ($p = 0.0197$ vs negative control). Histological examination revealed that higher doses of the extract restored pancreatic histoarchitecture, with intact acini cells and islets of Langerhans.

Conclusion: *Leonotis mollissima* aqueous leaf extract exhibits significant hypoglycemic and hypolipidemic effects in type 2 diabetic Wistar rats, supporting its traditional use. The extract's ability to improve glycemic control, lipid profiles, and pancreatic histoarchitecture suggests its potential as a therapeutic agent for managing diabetes and its complications. Further research is recommended to isolate active compounds and evaluate their efficacy in clinical trials.

Keywords: diabetes mellitus, *Leonotis mollissima*, hypoglycemic, hypolipemic, herbal medicine

Introduction

Diabetes mellitus, a metabolic disorder characterized by chronic hyperglycemia, has been documented since ancient times, with modern understanding revolutionized by insulin's discovery in 1921.^{1,2} Type 2 diabetes, driven by insulin resistance and environmental factors like obesity, accounts for over 90% of global diabetes cases.³ Its complications, including dyslipidemia and organ damage, exacerbate healthcare burdens, particularly in low-income regions where diagnosis and treatment remain inadequate.^{3,4}

The global burden of diabetes continues to rise, with over 537 million adults affected, many of whom remain undiagnosed particularly in low- and middle-income countries.^{3,4} In sub-Saharan Africa, limited access to conventional therapies and rising healthcare costs have driven increased reliance on traditional medicinal plants for glycemic control.⁵⁻⁹

Herbal medicines have re-emerged as cost-effective alternatives for type 2 diabetes management, with plants like *Momordica charantia* and *Allium sativum* demonstrating hypoglycemic properties.^{10,11} Ethnobotanical studies across Africa, including Uganda, have documented the use of numerous plant species for diabetes management, often prepared as decoctions or infusions.^{12–14} *Leonotis mollissima* (Lamiaceae family) is traditionally used for the management of various ailments including pain, arthritis, malaria and diabetes and is reported to contain bioactive compounds with potential therapeutic benefits.^{15,16} Bioactive compounds in its leaves, including flavonoids and alkaloids, suggest therapeutic potential, though limited evidence exists on its efficacy and safety in diabetes management.^{17,18}

This study investigates the effects of *Leonotis mollissima* leaf extract on type 2 diabetes, guided by the Health Belief Model.¹⁹ The model posits that health behaviors are influenced by perceived susceptibility, severity, benefits, barriers, self-efficacy, and cues to action.²⁰ With 54% of African diabetes cases undiagnosed and conventional therapies often unaffordable, exploring accessible alternatives like *L. mollissima* is critical.^{4,7} This underscores the need for accessible and affordable treatment options, such as herbal medicines, which are often preferred alternatives to conventional treatments. This study evaluates the leaf extract's effects on glycemic control, lipid profiles, and pancreatic histology in type 2 diabetes.

Material and Methods

Study Design

The study was an in vivo experiment.

Study Site

The study was carried out at Kampala International University – Western Campus (KIU-WC) located in Bushenyi district, Southwestern Uganda. Plant extraction was done at the KIU-WC Pharmacognosy Laboratory, and in vivo studies were done at the KIU-WC Animal Research Laboratory. The pancreatic tissue for histopathological analysis was processed immediately at the KIU-WC Histology Laboratory while the serum samples were analysed for lipid profile parameters at KIU-teaching hospital.

Plant Material Collection, Identification and Extract Preparation

Fresh *Leonotis mollissima* leaves were obtained from a farm in Nyakitunda Sub-county, Isingiro district and taxonomically identified by Dr. Eunice Olet at Mbarara University (Voucher number: NS 001). A voucher specimen was then prepared and deposited at the herbarium for future reference.

The leaf extract was prepared following a method described by Al-Dashti et al.²¹ Briefly, freshly collected leaves of *Leonotis mollissima* were dried under shade and then later ground using a mortar and pestle to produce a fine powder. The extraction was done by the maceration method where 1500g of the powder were added to fifteen liters of distilled water at room temperature in which the formed mixture was homogenized and extraction proceeded in the rotary shaker for 24 hours. Then, the mixture was sieved with a double muslin cloth and filtered using Whatman filter paper. The extract was then oven dried at 40°C, weighed and kept in a properly labelled sample bottles and stored at –4°C. The percentage yield was calculated as follows;

Percentage yield = (weight of extract powder/weight of the dried leaf powder) × 100.

Weight of the dried *Leonotis mollissima* leaf powder = 1500 g;

Weight of the extracted powder = 220.14 g;

The percentage yield was 14.7%.

Phytochemical Screening

The *Leonotis mollissima* aqueous leaf extract was qualitatively screened for phytochemical constituents such as alkaloids, flavonoids, tannins, reducing sugar, phenolic compounds, cardiac glycosides, and steroids using the methods described by Dubale et al.²²

Test for Tannins

For the determination of the presence of tannins, the ferric chloride test was used where to 1 mL of the extract, 3 drops of 0.1% ferric chloride solution were added and a brownish-green solution was formed which indicated the presence of tannins.

Test for Alkaloids

Alkaloids were screened for using the Mayer's test in which 1 mL of the extract was acidified with 1 mL of dilute hydrochloric acid. Then, 2 drops of Mayer's reagent were added and a cream-colored precipitate was formed which indicated the presence of alkaloids.

Test for Reducing Sugars

Five mL of Benedict's reagent were added to 1 mL of the extract and the mixture was boiled for 2 minutes. However, no precipitate was formed which indicated the absence of reducing sugars.

Test for Flavonoids

Flavonoids were assessed for by adding 2 drops of a 10% sodium hydroxide solution to 1 mL of the extract. This formed a yellow color that decolorized upon addition of dilute hydrochloric acid indicating the presence of flavonoids.

Test for Phenols

To 1 mL of the extract, 1 drop of 1% ferric chloride solution was added and the formation of a transient brownish-green solution indicated the presence of phenols.

Test for Steroids

To determine the presence of steroids, the extract was dissolved in 2 mL of chloroform, and an equal volume of concentrated sulfuric acid was added. A reddish-brown color was formed in the chloroform layer which indicated the presence of steroids.

Test for Phlobatanins

The phlobatanins were screened for using the acid precipitation test where 2 mL of the extract was boiled with 2 mL of 2% hydrochloric acid for 30 minutes. The formation of a red precipitate indicated the presence of phlobatanins.

Test for Cardiac Glycosides

A half a gram of the extract was dissolved in 2 mL of glacial acetic acid after which 1 drop of 2% ferric chloride was added. Then, concentrated sulfuric acid was carefully added to the mixture with the test tube slanted so as to form a layer. This led to the formation of a brown ring at the interface which indicated the presence of cardiac glycosides.

Experimental Animals, Housing and Feeding

A total of forty-eight (48) Wistar rats; 24 – male and 24 – female, 12 weeks old, weighing between 150–170g were used in the present study. The animals were acquired from the animal facility, of Kampala International University Western Campus. To identify the rats, a unique number was marked on the tail of each rat using a permanent marker. The rats were kept in a plastic cage in groups according to their dose levels. They were left to acclimatize for 14 days in the laboratory conditions prior to the experiment while under close monitoring and ensuring standard laboratory conditions of 12-hours light/ dark cycle, room temperature ($22 \pm 3^\circ\text{C}$) and relative humidity of $50 \pm 5\%$. The animals were fed on standard commercial dry rat pellets (Ngaano[®] feed company Ltd, Kampala –Uganda) throughout the experiment. Additionally, clean water was availed *ad-libitum*. The experimental study and animal handling followed the Guide for Care and Use of Laboratory Animals (National Research Council, 2010) and Animal Ethics Committee regulations of Kampala International University.

Induction of Type 2 Diabetes Mellitus and Treatment

The rats were randomly divided into six experimental groups of four rats of either sex each that is; normal control group, negative control group (distilled water 10 mg/kg), positive control group (glimepiride 5 mg/kg), low (250 mg/kg),

medium (500 mg/kg) and high (1000 mg/kg) dose of *Leonotis mollissima* leaf extract. The positive control group received glimepiride (5 mg/kg), a sulfonylurea antidiabetic drug that stimulates insulin secretion from pancreatic β -cells by inhibiting ATP-sensitive K^+ channels. Its application serves as a therapeutic benchmark to evaluate the efficacy of *Leonotis mollissima* extract. Type 2 diabetes mellitus was induced in Wistar rats using a two-step protocol according to a method by Gheibi et al.,²³ The rats were fed a calorically dense diet composed of 60% fat; 45% butter, 40% carbohydrate, 15% protein, 0.5% cholesterol for 14 days to induce insulin resistance. Following this, a single intraperitoneal dose of streptozotocin (STZ - 35 mg/kg) dissolved in citrate buffer (pH 4.5) was administered to destroy pancreatic β -cells. Diabetes was confirmed when fasting blood glucose levels exceeded 7 mmol/L after 72 hours using an On Call[®] Plus blood glucose meter (ACON Laboratories, Inc., USA).

With the exception of the normal control group, all the other groups contained type 2 diabetic Wistar rats and were treated according to their respective groupings. Administration of both glimepiride and *Leonotis mollissima* was done by oral gavage after measurement of the rats' body weight. The body weights and fasting blood glucose levels of each rat were measured on weekly basis and also on the day of sacrifice.

Collection of Samples and Measurement of Study Parameters

Tissue Harvest and Preparation

At completion of the study, and after an over-night fast, animals were anesthetized with halothane. Blood samples were collected through cardiac puncture from all of the rats while the pancreas was removed for histological analysis. The pancreas was examined for gross morphological changes before it was fixed in 10% neutral formaldehyde buffer for 5 days for histopathological studies.

Histopathological Examination

Tissue Processing

The tissue samples obtained were processed at the Histology laboratory within the Department of Anatomy, Faculty of Biomedical Sciences at Kampala International University. Each of the pancreas tissue samples, collected from the different treatment groups were individually fixed in 10% neutral buffered formalin. After fixation, the tissues were rinsed overnight in running water to eliminate excess fixative and dehydrated using increasing ethanol concentrations.^{24,25} Following dehydration, the tissues were passed through a solution of xylene to remove residual ethanol and facilitate the infiltration of molten paraffin wax (at 55°C). These wax-impregnated tissues were then embedded into paraffin blocks, labeled appropriately and left to dry at room temperature. The labeled tissue blocks were subsequently sliced into sections, with a thickness of 5–6 μ m, using a Leica Rotary Microtome (Leica Rm2125RT, Model Rm2125, China) and floated on a tissue flotation water bath at a controlled temperature of 20°C, allowing the paraffin wax-impregnated tissues to stretch appropriately. The stretched ribbons were then carefully transferred onto glass microscopic slides and kept in a warm oven overnight to promote adhesion of the tissue slices to the slides. Subsequently, the slides were allowed to cool at room temperature, making them ready for the subsequent standard staining processes.^{24,25}

Tissue Staining

Prior to the tissue staining procedure, the sections underwent deparaffinization through treatment with xylene. Subsequently, the tissues were hydrated in a sequential manner by passing them through solutions of decreasing alcohol concentrations. Following this, the slides were subjected to a thorough rinse in distilled water, after which they were exposed to the Harris' hematoxylin stain. Once stained with Harris' hematoxylin, the slides were washed in tap water and immersed in 1% acid alcohol to facilitate differentiation and the removal of excess stain. The sections were then briefly rinsed in running tap water to eliminate any surplus acid. Following this step, the slides were immersed in a bluing solution, followed by a counterstain using eosin. The sections that had undergone hematoxylin and eosin (H and E) staining were subsequently dehydrated by sequentially passing them through increasingly concentrated ethyl alcohol solutions. Finally, these prepared slides were mounted and sealed with glass cover slips.^{24,25}

Microscopy and Photomicrography

Microscopic slides of the pancreas were examined carefully under a compound light microscope at the Histology laboratory, Department of Anatomy, Faculty of Biomedical Sciences, Kampala International University. Slides from the extract treated groups were evaluated for any toxic insult to the organs compared to slides from their respective control groups. Finally, photomicrographs of selected slides were taken using a light microscope (Olympus BH2) mounted with a Nikon Digital Sight DS-L1 (Nikon Corporation, Japan).

Lipid Profile Analysis

At completion of the study, blood samples were collected through cardiac puncture under halothane anesthesia. 3 mL of blood was put in a non-heparinized vacutainer for lipid profile analysis using an automated biochemistry analyzer.

Determination of Glycemic Parameters

Fasting blood glucose was measured weekly using glucometers. Oral glucose tolerance tests involved administering 2 g/kg glucose orally and measuring blood glucose at 0, 30, 60, 90, and 120 minutes. Percentage reductions in the OGTT levels were calculated using $[(\text{OGTT}_{\text{negative control group}} - \text{OGTT}_{\text{test group}}) / \text{OGTT}_{\text{negative control group}}] * 100$. Glycated hemoglobin (HbA1c) was quantified via ion-exchange chromatography at study termination.

Data Management and Analysis

Data was analyzed using Graph Pad Prism (Version 9.5.1). Data obtained from the glycemic and lipid profile parameters was analyzed by determining differences between groups by one-way ANOVA followed by Turkey's Honest Post-hoc test. Results are presented as mean $\pm$ standard error of the mean (SEM), and values at $p \leq 0.05$ were considered statistically significant.

Results

Phytochemical Composition of *Leonotis mollissima* Aqueous Leaf Extract

Qualitative phytochemical analysis confirmed the presence of tannins, phenols, flavonoids, phlobatannins, cardiac glycosides, steroids, and alkaloids, whereas reducing sugars were absent (Table 1).

Glycemic Effect of the Aqueous Leaf Extract of *Leonotis mollissima* in Type 2 Diabetic Wistar Rats

Effect of the Aqueous Leaf Extract of *Leonotis mollissima* on the Fasting Blood Sugar Levels in Type 2 Diabetic Wistar Rats

Fasting blood sugar (FBS) reflects baseline glycemia after an 8–12 hour fast, providing insight into hepatic glucose production and insulin sensitivity. In diabetes management, FBS monitoring is critical for assessing metabolic control and treatment efficacy. This study determined FBS weekly to evaluate sustained glycemic improvements.

Table 1 Phytochemical Profile of *Leonotis mollissima* Aqueous Leaf Extract

Phytochemical	Qualitative Test Result
Tannins	+
Phenols	+
Flavonoids	+
Phlobatannins	+
Cardiac glycosides	+
Steroids	+
Reducing sugars	–
Alkaloids	+

Note: + indicates presence; – indicates absence.

In male diabetic rats, FBS levels were markedly elevated in the negative control, positive control (glimepiride (5 mg/kg), and *Leonotis mollissima* (250, 500, and 1000 mg/kg) groups ($p = 0.0017$, $p = 0.0079$, $p = 0.0019$, $p = 0.0332$, respectively) in comparison to the normal control group at the initial time point. After one week, the leaf extract of *Leonotis mollissima* (250, 500, and 1000 mg/kg) kept down fasting blood sugar FBS levels compared to the negative control. The results in Table 2 also demonstrated that the fasting blood sugar FBS levels in male diabetic rat groups treated with *Leonotis mollissima* (1000 mg/kg) and glimepiride (5 mg/kg) reached 8.6 ± 1.69 mmol/L and 8.28 ± 3.02 mmol/L, respectively.

Furthermore, in male diabetic rats, FBS levels remained elevated in the negative control group during Week 2 (10.5 ± 1.68 mmol/L) and Week 3 (10.58 ± 2.96 mmol/L). Treatment with *Leonotis mollissima* (500 mg/kg) progressively reduced FBS from Week 1 (9.68 ± 0.6 mmol/L) to Week 3 (7.65 ± 0.32 mmol/L), demonstrating dose-dependent efficacy. The 1000 mg/kg group showed accelerated improvement, reaching 7.1 ± 0.52 mmol/L by Week 3, nearing glimepiride's effect (6.08 ± 0.64 mmol/L).

By the end of the 4th week, FBS levels remained significantly elevated in the negative control group ($p = 0.0006$). When compared to the negative control group (FBS: 10.98 ± 1.2 mmol/L), treatment with glimepiride (5 mg/kg) and *Leonotis mollissima* (1000 mg/kg) over 28 days led to a notable reduction in FBS levels ($p = 0.0052$ and $p = 0.0429$, respectively) to 5.23 ± 0.28 and 6.5 ± 0.67 mmol/L (Table 2).

For female diabetic rats, initial FBS levels were significantly higher in the negative control group and treatment groups (glimepiride 5 mg/kg, *Leonotis mollissima* 250 mg/kg, 500 mg/kg, and 1000 mg/kg) with p -values of 0.196, 0.0343, 0.0330, and 0.0368, respectively when compared to the normal control. At the end of week 1, all the doses of *Leonotis mollissima* reduced FBS when compared with the negative control (9.99 ± 0.12 mmol/L), with the 1000 mg/kg dose achieving 8.55 ± 1.95 mmol/L. At the end of week 2, the 500 mg/kg (8.58 ± 0.18 mmol/L) and 1000 mg/kg (7.1 ± 3.4 mmol/L) dose groups of *Leonotis mollissima* showed superior glucose-lowering when compared to their effect in week 1. The FBS declined further in the *Leonotis mollissima* 1000 mg/kg group (6.85 ± 3.45 mmol/L), outperforming glimepiride (5 mg/kg) (7.53 ± 1.63 mmol/L).

Nevertheless, the negative control group maintained substantially higher FBS levels ($p = 0.0081$) than the normal control group at the fourth week (Table 2). The leaf extract of *Leonotis mollissima*, at concentrations of 250 mg/kg, 500 mg/kg, and 1000 mg/kg, was able to decrease the level of FBS in the blood of female diabetic rats to $7.55 \pm$

Table 2 Effect of *Leonotis mollissima* Aqueous Leaf Extract on the Serum FBS Levels of Type 2 Diabetic Male and Female Wistar Rats

Wistar Rats Groups	Fasting Blood Sugar (mmol/L)				
	Baseline	Week 1	Week 2	Week 3	Week 4
Males					
Normal control	4.48 ± 0.25	4.43 ± 0.28	4.3 ± 0.11	4.5 ± 0.071	4.08 ± 0.17
Negative control	$9.18 \pm 2.08^*$	9.98 ± 1.52	10.5 ± 1.68	10.58 ± 2.96	$10.98 \pm 1.2^*$
Positive control	$10.83 \pm 0.61^*$	8.28 ± 3.02	7.73 ± 0.35	6.08 ± 0.64	$5.23 \pm 0.28^{\#}$
<i>L. mollissima</i> 250 mg/kg	$10 \pm 1.82^*$	9.55 ± 1.51	9.43 ± 0.19	8.58 ± 0.39	8.28 ± 0.3
<i>L. mollissima</i> 500 mg/kg	$10.78 \pm 0.76^*$	9.68 ± 0.6	8.2 ± 0.42	7.65 ± 0.32	7.48 ± 0.27
<i>L. mollissima</i> 1000 mg/kg	$9.13 \pm 1.68^*$	8.6 ± 1.69	7.93 ± 0.62	7.1 ± 0.52	$6.5 \pm 0.67^{\#}$
Females					
Normal control	4.7 ± 0.45	4.83 ± 0.2	4.63 ± 0.06	4.95 ± 0.07	4.7 ± 0.15
Negative control	$9.75 \pm 0.27^*$	9.99 ± 0.12	10.08 ± 0.19	10.63 ± 0.09	$10.88 \pm 0.08^*$
Positive control	$10.3 \pm 2.71^*$	9.55 ± 0.32	8.5 ± 1.53	7.53 ± 1.63	6.83 ± 1.87
<i>L. mollissima</i> 250 mg/kg	$9.9 \pm 0.43^*$	8.73 ± 0.19	8.08 ± 0.45	7.73 ± 0.19	7.55 ± 0.29
<i>L. mollissima</i> 500 mg/kg	$9.93 \pm 0.23^*$	8.88 ± 0.29	8.58 ± 0.18	7.38 ± 0.3	6.85 ± 0.85
<i>L. mollissima</i> 1000 mg/kg	$9.85 \pm 0.41^*$	8.55 ± 1.95	7.1 ± 3.4	6.85 ± 3.45	6.38 ± 3.18

Notes: Data are expressed as Mean $\pm$ SEM, $n = 4$; * - $p < 0.05$ vs normal control group, $^{\#}$ - $p < 0.05$ vs negative control group (male and females separated). Normal control represents a Wistar rats group that is not infected with diabetes type 2; negative control represents a Wistar rats group that is infected with diabetes type 2; positive control represents a Wistar rats group with diabetic type 2 but treated with glimepiride (5mg/kg).

0.29 mmol/L, 6.85 ± 0.85 mmol/L, and 6.38 ± 3.18 mmol/L. Furthermore, it was found that the efficacy of *Leonotis mollissima* at a dose of 1000 mg/kg in reducing FBS levels is almost the same as that of glimepiride (5 mg/kg), which is 6.83 ± 1.87 mmol/L. In general, the activity leaf extract of *Leonotis mollissima*, in lowering FBS levels at concentrations of 250 mg/kg, 500 mg/kg, and 1000 mg/kg for female diabetic rats is best than male diabetic rats. The current study revealed that the leaf extract of *Leonotis mollissima* is often more efficient in reducing fasting blood sugar levels in female diabetic rats compared to male diabetic rats at doses of 250 mg/kg, 500 mg/kg, and 1000 mg/kg.

Effect of the Aqueous Leaf Extract of *Leonotis mollissima* on the Oral Glucose Tolerance Test (OGTT) Levels in Type 2 Diabetic Wistar Rats

The oral glucose tolerance test (OGTT) assesses the body's capacity to regulate blood glucose after a controlled glucose load. It evaluates insulin sensitivity, β -cell function, and glucose disposal. In diabetes research, OGTT identifies impaired glucose tolerance and quantifies therapeutic efficacy.

Following the administration of 40% glucose, OGTT levels were measured at 30, 60, 90, and 120 minutes in both male and female diabetic rats. Results indicate that in males after 120 minutes, glimepiride (5 mg/kg) caused a 62.6% reduction in the OGTT levels (5.53 ± 0.52 mmol/L vs negative control 14.8 ± 0.8 mmol/L; $p < 0.0001$). The *Leonotis mollissima* aqueous leaf extract (250, 500, and 1000 mg/kg) also caused a significant dose dependent reduction (42.7%, 51.4%, and 53.5%; $p < 0.0001$ respectively) in OGTT levels compared to the negative control group (Table 3).

Similarly, for female diabetic rats after 120 minutes, glimepiride (5 mg/kg) caused a 56.6% reduction in the OGTT levels (6.9 ± 0.5 mmol/L vs negative control 15.9 ± 0.7 mmol/L; $p < 0.0001$). Treatment with the *Leonotis mollissima* aqueous leaf extract (250, 500, and 1000 mg/kg) led to a significant dose dependent reduction (48.9%, 55.9%, 59.1%; $p < 0.0001$) in OGTT levels when compared to the negative control group (Table 3).

Effect of the Aqueous Leaf Extract of *Leonotis mollissima* on the Glycated Haemoglobin Levels in Type 2 Diabetic Wistar Rats

Glycated hemoglobin forms when prolonged hyperglycemia promotes non-enzymatic hemoglobin glycosylation. Elevated HbA1c (>6.5%) indicates suboptimal glycemic control and correlates with diabetes complications. In this study, HbA1c was measured at the end of the study (day 28) to evaluate chronic glucose management over a biologically

Table 3 Effect of *Leonotis mollissima* Aqueous Leaf Extract on the OGTT Levels of Type 2 Diabetic Male and Female Wistar Rats

Wistar Rats Groups	Oral glucose tolerance test (mmol/L)				
	0 Minute	30 Minutes	60 Minutes	90 Minutes	120 Minutes
Males					
Negative control	10.98 ± 1.2	16.42 ± 1.05	16.15 ± 1.2	15.3 ± 0.9	14.8 ± 0.8
Positive control	5.23 ± 0.28	8.53 ± 1.83	7.5 ± 0.38	6.38 ± 0.74	$5.53 \pm 0.52^{\#}$
<i>L. mollissima</i> 250 mg/kg	8.28 ± 0.3	9.35 ± 0.51	9 ± 0.94	8.63 ± 0.7	$8.48 \pm 0.71^{\#}$
<i>L. mollissima</i> 500 mg/kg	7.48 ± 0.27	9.5 ± 0.78	8.48 ± 0.74	8.18 ± 0.62	$7.2 \pm 0.53^{\#}$
<i>L. mollissima</i> 1000 mg/kg	6.5 ± 0.67	8.9 ± 0.2	8.53 ± 2	7.55 ± 0.73	$6.88 \pm 1.65^{\#}$
Females					
Negative control	10.88 ± 0.08	17.68 ± 1.89	17.1 ± 0.72	16.65 ± 0.69	15.9 ± 0.7
Positive control	6.83 ± 1.87	9.9 ± 0.8	8.7 ± 0.7	7.3 ± 0.6	$6.9 \pm 0.5^{\#}$
<i>L. mollissima</i> 250 mg/kg	7.55 ± 0.29	10.93 ± 0.84	8.55 ± 0.62	8.28 ± 0.61	$8.13 \pm 0.63^{\#}$
<i>L. mollissima</i> 500 mg/kg	6.85 ± 0.85	9.3 ± 0.93	8.3 ± 0.49	7.88 ± 0.4	$7 \pm 0.3^{\#}$
<i>L. mollissima</i> 1000 mg/kg	6.38 ± 0.18	9.65 ± 1.76	8.08 ± 0.76	7.7 ± 0.5	$6.5 \pm 0.5^{\#}$

Notes: Data are expressed as Mean $\pm$ SEM, $n = 4$; $^{\#} - p < 0.05$ vs negative control group (male and females separated). Normal control represents a Wistar rats group that is not infected with diabetes type 2; negative control represents a Wistar rats group that is infected with diabetes type 2; positive control represents a Wistar rats group with diabetic type 2 but treated with glimepiride (5mg/kg).

relevant period. Given the 60-day lifespan of rat erythrocytes, day 28 captures glycemic control across approximately 50% of the red blood cell lifecycle, providing a validated index of sustained glucose management.

The negative control group, along with the *Leonotis mollissima* 250 mg/kg and 500 mg/kg groups, showed significantly higher glycated hemoglobin levels ($p < 0.0001$ and $p = 0.0006$) compared to the normal control group. However, treatment with glimepiride (5 mg) and *Leonotis mollissima* (500 mg/kg and 1000 mg/kg) resulted in a significant reduction in glycated hemoglobin levels (50.9%; $p < 0.0001$, 29.3%; $p = 0.0004$, and 48.5%; $p < 0.0001$, respectively) compared to the negative control group (Table 4).

As reported in Table 4, the Wistar rats groups infected with diabetic type 2 exposed to 250 mg/kg and 500 mg/kg concentration of *Leonotis mollissima* demonstrated notable increase in the glycated hemoglobin levels ($p < 0.0001$ and $p = 0.0094$) compared to the group of diabetic 2 Wistar rats treated with the 5mg/Kg of Glimepiride. Furthermore, both the glimepiride (5 mg/Kg) and *Leonotis mollissima* (1000 mg/kg) assist to reduce the level of Glycated haemoglobin to $4.95 \pm 0.4\%$, and 5.2 ± 0.3 , respectfully.

Effect of *Leonotis mollissima* Aqueous Leaf Extract on the Lipid Profile of Type 2 Diabetic Wistar Rats

Lipid profiles (total cholesterol, triglycerides, LDL, HDL) are key cardiovascular risk indicators. Dyslipidemia characterized by elevated LDL/triglycerides and low HDL accelerates atherosclerosis in diabetes. Type 2 diabetes induces dyslipidemia via insulin resistance, which enhances lipolysis and hepatic VLDL secretion. This elevates circulating triglycerides and LDL while suppressing HDL. Consequently, lipid profile management is essential to reduce cardiovascular mortality in diabetic patients.

In male diabetic rats, cholesterol, triglyceride, and LDL-cholesterol levels were significantly higher in the negative control group ($p = 0.0020$, $p = 0.0023$, and $p = 0.0224$, respectively) compared to the normal control group. Treatment with glimepiride (5 mg), *Leonotis mollissima* (500 mg/kg), and 1000 mg/kg significantly reduced plasma cholesterol levels ($p = 0.0194$, $p = 0.0458$, and $p < 0.0001$, respectively) (Table 5).

Table 4 Effect of *Leonotis mollissima* Aqueous Leaf Extract on the Glycated Haemoglobin Levels of Type 2 Diabetic Wistar Rats

Wistar Rats Groups	Glycated Haemoglobin (%)
Normal control	4.3 ± 0.25
Negative control	$10.1 \pm 0.46^*$
Positive control (Glimepiride 5 mg)	$4.95 \pm 0.4^{\#}$
<i>L. mollissima</i> 250 mg/kg	$8.47 \pm 0.66^{* \beta}$
<i>L. mollissima</i> 500 mg/kg	$7.14 \pm 0.62^{* \# \beta}$
<i>L. mollissima</i> 1000 mg/kg	$5.2 \pm 0.3^{\#}$

Notes: Data are expressed as Mean $\pm$ SEM, $n = 8$; * - $p < 0.05$ vs normal control group, $\#$ - $p < 0.05$ vs negative control group, β - $p < 0.05$ vs positive control group. Normal control represents a Wistar rats group that is not infected with diabetes type 2; negative control represents a Wistar rats group that is infected with diabetes type 2; positive control represents a Wistar rats group with diabetic type 2 but treated with glimepiride (5mg/kg).

Table 5 Effect of *Leonotis mollissima* Aqueous Leaf Extract on the Lipid Profile of Type 2 Diabetic Male and Female Wistar Rats

Wistar Rats Groups	Lipid Profile Parameters			
	Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL-Cholesterol (mg/dL)	HDL-Cholesterol (mg/dL)
Males				
Normal control	130.17 ± 10.08	100.04 ± 10.01	70.79 ± 7.44	45.56 ± 4.23
Negative control	$180.72 \pm 12.03^*$	$150.03 \pm 3.42^*$	$110.24 \pm 9.29^*$	35.52 ± 4.97
Positive control	$140.56 \pm 12.18^{\#}$	$110.51 \pm 18.76^{\#}$	80.25 ± 8.38	42.01 ± 5.18
<i>L. mollissima</i> 250 mg/kg	165.33 ± 8.49	130.58 ± 10.92	95.78 ± 10.41	40.14 ± 0.48
<i>L. mollissima</i> 500 mg/kg	$145.04 \pm 8.21^{\#}$	126.04 ± 20.64	85.71 ± 3.66	43.12 ± 5.32

(Continued)

Table 5 (Continued).

Wistar Rats Groups	Lipid Profile Parameters			
	Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL-Cholesterol (mg/dL)	HDL-Cholesterol (mg/dL)
<i>L. mollissima</i> 1000 mg/kg	108.69 ± 11.03 [#]	103.39 ± 7.13 [#]	75.72 ± 8.25	45.29 ± 5.89
Females				
Normal control	123.36 ± 10.59	95.79 ± 9.33	65.41 ± 7.07	48.8 ± 7.55
Negative control	175.86 ± 10.19 *	145.95 ± 14.41 *	105.89 ± 11.09 *	38.61 ± 4.22
Positive control	135.95 ± 12.16 [#]	105.61 ± 10.23 [#]	75.79 ± 9.2	45.24 ± 6.1
<i>L. mollissima</i> 250 mg/kg	155.65 ± 13.68	125.86 ± 12.92	90.41 ± 10.67	43.26 ± 4.36
<i>L. mollissima</i> 500 mg/kg	145.68 ± 12.96	115.65 ± 12.56	82.74 ± 7.67	46.01 ± 7.28
<i>L. mollissima</i> 1000 mg/kg	130.16 ± 5.53 [#]	100.41 ± 17 [#]	70.09 ± 3.93	48.78 ± 5.23

Notes: Data are expressed as Mean ± SEM, n = 5; * - $p < 0.05$ vs normal control group, [#] - $p < 0.05$ vs negative control group (male and females separated). Normal control represents a Wistar rats group that is not infected with diabetes type 2; negative control represents a Wistar rats group that is infected with diabetes type 2; positive control represents a Wistar rats group with diabetic type 2 but treated with glimepiride (5mg/kg).

Similarly, glimepiride (5 mg) and *Leonotis mollissima* (1000 mg/kg) significantly lowered plasma triglyceride levels ($p = 0.0194$ and $p < 0.0001$, respectively) (Table 5).

In female diabetic rats, cholesterol, triglyceride, and LDL-cholesterol levels were significantly elevated in the negative control group ($p = 0.0020$, $p = 0.0033$, and $p = 0.0243$, respectively) compared to the normal control group. Treatment with glimepiride (5 mg) and *Leonotis mollissima* (1000 mg/kg) significantly reduced cholesterol and triglyceride levels ($p = 0.0271$ and $p = 0.0086$ for cholesterol; $p = 0.0250$ and $p = 0.0082$ for triglycerides) (Table 5).

The 1000 mg/kg *Leonotis mollissima* dose in males significantly reduced total cholesterol (108.69 ± 11.03 mg/dL) and LDL (75.72 ± 8.25 mg/dL), with effects surpassing females. However, triglyceride reduction was more pronounced in females (100.41 ± 17 mg/dL at 1000 mg/kg vs males: 103.39 ± 7.13 mg/dL). HDL improvement was comparable across sexes. Thus, *Leonotis mollissima* exerted stronger triglyceride-lowering effects in females and more robust cholesterol/LDL reduction in males.

Effect of *Leonotis mollissima* Aqueous Leaf Extract on the Histology of the Pancreatic Islets in Type 2 Diabetic Wistar Rats

Histological analysis revealed that the control group (Standard rat feed + distilled water) exhibited normal pancreatic architecture, including well-preserved acini cells and islets of Langerhans (Figure 1A). Conversely, negative control rats (HFD + 35 mg/kg STZ + distilled water) exhibited reduced and vacuolated islet cells and degenerated acini cells (Figure 1B).

Treatment with glimepiride (5 mg/kg) resulted in restored pancreatic architecture, with intact acini cells and islets of Langerhans (Figure 1C). Among the *Leonotis mollissima*-treated groups, the 250 mg/kg dose led to partial improvement (Figure 1D), while the 500 mg/kg and 1000 mg/kg doses exhibited greater restoration of pancreatic structure (Figures 1E and F).

Leonotis mollissima (1000 mg/kg) matches glimepiride's efficacy in the restoration of the pancreatic histoarchitecture while also having multitarget effects on lipid profiles, oxidative stress and also avoidance of sulfonylurea-associated risks like hypoglycemia and β -cell exhaustion.

Discussion

The phytochemical profile of the extract revealed the presence of tannins, phenols, flavonoids, steroids, and alkaloids which are compounds widely recognized for their hypoglycemic and hypolipidemic properties.^{26,27} These findings are consistent with previous reports on the phytochemical composition of *Leonotis mollissima*.²⁸ The absence of reducing sugars suggests that the observed therapeutic effects may stem from synergistic interactions among the detected phytochemicals rather than isolated compounds. This aligns with studies on other plant-derived polyphenols, such as

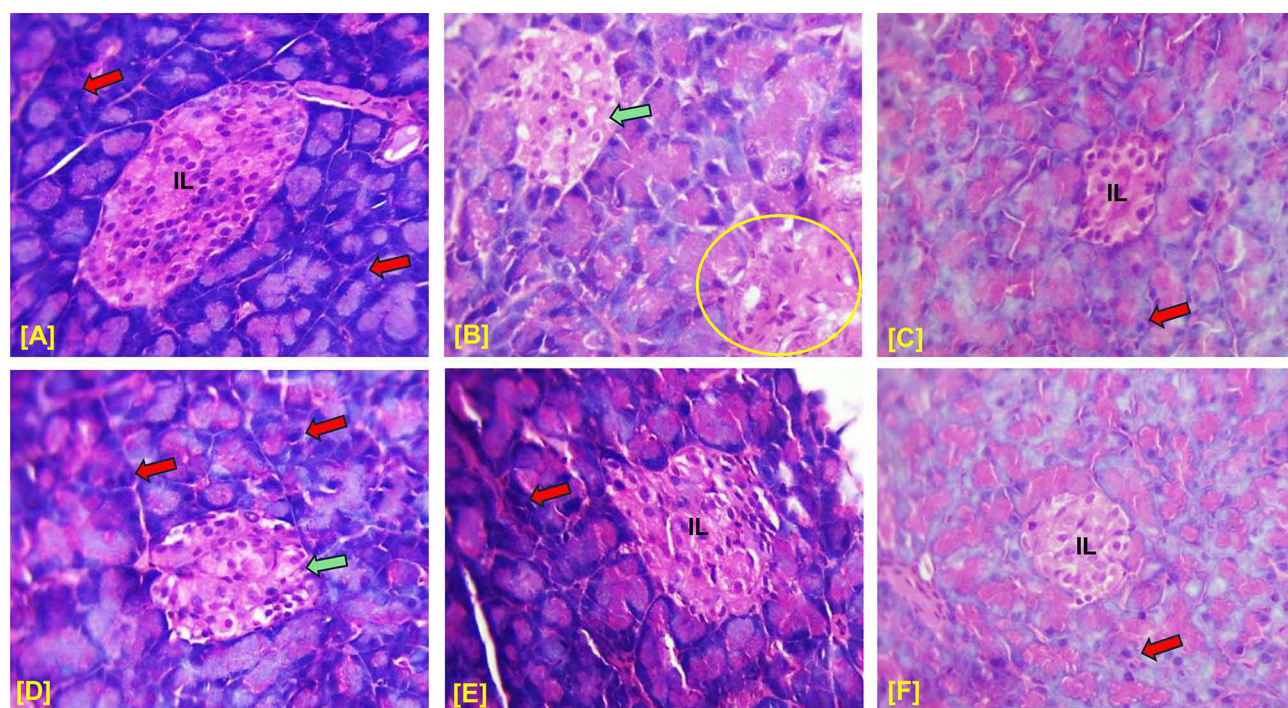


Figure 1 Photomicrograph of the pancreas (A–F) from the different treatment groups (H & E; $\times 400$). (A) Standard rat feed + distilled water (10 mg/kg), (B) HFD + 35 mg/kg b.wt STZ + distilled water (10mg/kg), (C) - HFD + 35 mg/kg b.wt STZ + Glimepiride (5mg/kg), (D) HFD + 35 mg/kg b.wt STZ + 250 mg/kg of *Leonotis mollissima* aqueous leaf extract, (E) HFD + 35 mg/kg b.wt STZ + 500 mg/kg of *Leonotis mollissima* aqueous leaf extract, (F) HFD + 35 mg/kg b.wt STZ + 1000 mg/kg of *Leonotis mollissima* aqueous leaf extract. IL - islet of Langerhans. The red arrow shows acini cells; green arrow shows reduced and vacuolated islet cells, while the yellow circle shows degenerated acini cells. (H & E; $\times 400$).

those in *Serenoa repens* and *Urtica dioica*, where multi-component interactions enhance therapeutic efficacy in hyperglycemic management.²⁹

This study demonstrated a significant reduction in fasting blood sugar levels and improved outcomes in the oral glucose tolerance test in diabetic rats administered with *Leonotis mollissima* extract. The efficacy of the 1000 mg/kg dose was comparable to that of glimepiride, a commonly used sulfonylurea. These findings are consistent with research on other species from the Lamiaceae family, such as *Ocimum basilicum*, which is known to regulate blood glucose through flavonoid-induced AMPK activation.²⁸

Additionally, the ability of *Leonotis mollissima* to lower glycated haemoglobin levels suggests its potential for long-term glucose control. Similar hypoglycemic effects have been observed in other herbal extracts, including *Passiflora suberosa* and *Phaseolus vulgaris*.²⁶ These effects may be linked to polyphenolic compounds within the extract, which could inhibit dipeptidyl peptidase-4 (DPP-4), thereby enhancing insulin secretion and function.²⁶

Sex-based differences in response to *Leonotis mollissima* were also examined in this study. Both male and female diabetic rats showed significant reductions in FBS and OGTT values upon treatment, indicating that the extract is effective across sexes. While the 1000 mg/kg dose significantly reduced FBS in males, its effect in females lacked statistical significance. Notably, glimepiride when compared to the negative control group also showed weaker FBS reduction in females. This aligns with sex-based metabolic differences where females exhibit higher insulin sensitivity and GLUT4 expression, potentially masking drug efficacy at lower glucose levels. Furthermore, estrogen enhances pancreatic β -cell function, amplifying endogenous glucose regulation in diabetic females. Thus, females may require lower therapeutic thresholds than males to achieve statistical significance in FBS reduction.²⁷

Furthermore, the study revealed notable improvements in lipid profiles, with a reduction in total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels. This aligns with findings on medicinal plants such as *Momordica charantia* and *Camellia sinensis*, which have demonstrated lipid-lowering properties.³⁰ The observed

hypolipidemic effects of *Leonotis mollissima* may be attributed to its role in regulating lipid metabolism and preventing lipid peroxidation, likely due to its polyphenolic composition.²⁷

The reduction in lipid markers suggests that *Leonotis mollissima* may aid in managing diabetes-related dyslipidemia, potentially lowering the cardiovascular risks associated with diabetes. Comparable effects have been observed in other plant-based therapies, such as *Allium sativum* and *Nigella sativa*, which also exhibit lipid-modulating properties.³¹

Regarding lipid metabolism, both male and female rats experienced significant decreases in cholesterol, triglycerides, and LDL levels following extract treatment. However, lipid reduction appeared slightly greater in male rats, a trend that aligns with literature discussing sex-specific differences in response to lipid-lowering agents.³²

The therapeutic effects of *Leonotis mollissima* are likely associated with its rich content of flavonoids, phenolics, and tannins, which possess potent antioxidant properties. These compounds help mitigate oxidative stress, a major contributor to diabetes progression. By neutralizing free radicals and enhancing the body's antioxidant defenses, these phytochemicals may protect pancreatic β -cells and support insulin function, as suggested by prior research on flavonoid-rich plants.³³

Additionally, improvements in glycemic control and lipid metabolism may stem from tannins suppressing SREBP-1c, downregulating lipogenic enzymes, and reducing LDL and triglycerides. The co-occurrence of alkaloids and steroids has been shown to amplify improvements in glycemic control and lipid metabolism via PI3K/Akt signaling, explaining superior outcomes at higher doses.³⁴

Histological analysis of the control group (Standard rat feed + distilled water) revealed intact pancreatic architecture, including well-preserved acini cells and islets of Langerhans (Figure 1A). This confirms that standard diet and water did not induce any pathological changes, providing a baseline for comparison. This observation aligns with previous studies that established normal pancreatic histology in rodent models.³⁵

On the contrary, diabetic rats exposed to a high-fat diet (HFD) and streptozotocin (STZ) exhibited significant pancreatic damage, including vacuolated islet cells and degenerated acini cells (Figure 1B). This aligns with findings that STZ selectively destroys pancreatic β -cells, impairing insulin secretion and inducing hyperglycemia.²³ The observed deterioration in acini cells also suggests that diabetes negatively impacts exocrine pancreatic function, a phenomenon previously documented.²³

Treatment with glimepiride led to the restoration of normal pancreatic architecture, as evidenced by the presence of intact acini cells and islets of Langerhans (Figure 1C). This suggests that glimepiride mitigates diabetes-induced pancreatic damage, possibly through its hypoglycemic and β -cell protective effects.³⁶

Among *Leonotis mollissima*-treated groups, the 250 mg/kg dose resulted in partial improvement in pancreatic histology (Figure 1D), while higher doses (500 mg/kg and 1000 mg/kg) led to substantial restoration of islet structure (Figures 1E and 1F). This dose-dependent improvement suggests that *Leonotis mollissima* possesses protective and regenerative effects on pancreatic tissue, likely due to its hypoglycemic and antioxidant properties. These results align with previous studies on medicinal plants such as *Moringa oleifera* and *Gymnema sylvestre*, which have demonstrated β -cell protection and improved pancreatic function in diabetic models.^{37,38}

The improved histological findings at higher doses reinforce the growing evidence supporting plant-based therapies for diabetes management. The presence of bioactive compounds like flavonoids, and phenols may contribute to β -cell function enhancement and tissue repair, by reducing oxidative stress via Nrf2 pathway activation, preventing STZ-induced apoptosis.³⁹ Additionally, the antioxidant properties of *Leonotis mollissima* may be instrumental in countering diabetes-induced oxidative damage, a key factor in β -cell dysfunction and apoptosis.³²

Conclusion

The findings from this study indicate that *Leonotis mollissima* leaf extract exhibits significant blood glucose-lowering and lipid-modulating effects in type 2 diabetic Wistar rats. The presence of flavonoids and phenolics likely contributes to these therapeutic benefits, suggesting that the extract could serve as a natural alternative or adjunct therapy for diabetes management.

Furthermore, the histological results indicate that *Leonotis mollissima* can ameliorate pancreatic damage, particularly at higher doses. *Leonotis mollissima* (1000 mg/kg) exhibits comparable efficacy to glimepiride in glycemic control, lipid

modulation, and pancreatic restoration, with added advantages in sex-specific optimization where lower doses are effective in females and holistic management of diabetic complications via antioxidant and hypolipidemic actions.

These findings highlight the need for further research into active compound isolation, mechanistic studies and toxicological profiling to further exploit its potential clinical applications for diabetes treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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