RESEARCH ARTICLE

Exploring the Therapeutic Potential of *Lepidagathis pungens* Nees Extracts as Novel Therapy Options in Streptozotocin and Nicotinamide-Induced Diabetes in Albino Wistar Rats

Jothilakshmi R*, Srinivasan R

Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

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ABSTRACT

Diabetes mellitus remains a global health concern, necessitating innovative therapeutic approaches. This study explores the antidiabetic potential of aqueous and methanol extracts from *Lepidagathis pungens* Nees in albino Wistar rats induced with diabetes. Diabetes induction involves the administration of streptozotocin (STZ) and nicotinamide (NIC), mimicking pathological conditions observed in human diabetes. The study employed aqueous and methanol extracts of *L. pungens* Nees alongside a standard drug, glibenclamide. Diabetes induction was achieved through intraperitoneal injection of STZ and NIC. Extracts and the standard drug were orally administered, and various parameters, including blood glucose levels, body weight changes, insulin and hemoglobin levels, as well as liver and lipid profiles, were monitored at specified intervals. Furthermore, liver and pancreas tissues were evaluated histopathologically. In comparison to the diabetic group, both aqueous and methanol extracts demonstrated significant antidiabetic activity (p <0.001), with effects comparable to or better than the standard drug. A remarkable improvement in insulin and hemoglobin levels was observed, along with significant improvements in blood glucose levels and body weight changes. Furthermore, the extracts demonstrated positive effects on liver and lipid profiles, exhibiting potential to mitigate diabetes-induced complications. Histopathological studies revealed protective effects on liver and pancreas tissues, supporting the extracts' therapeutic efficacy. In STZ- and NIC-induced diabetic rats, *L. pungens* Nees extracts show promising antidiabetic activity. The extracts demonstrated significant improvements in various physiological parameters, suggesting their potential as alternative or adjunctive therapies in the management of diabetes. Further research and clinical investigations are warranted to elucidate the underlying mechanisms and translate these findings into practical therapeutic applications.

Keywords: *Lepidagathis*, Streptozotocin, Antidiabetic activity, Insulin non-dependent, Nicotinamide.

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INTRODUCTION

Globally, diabetes stands among the top six leading causes of mortality, giving rise to various systemic complications. α-glucosidase inhibitors, sulfonyl ureas, biguanides, and thiazolidinediones are some of the most common agents that are used for treating diabetes mellitus. Nevertheless, systemic disorder treatment is challenged by the development of adverse events. Many pharmaceutical companies and research institutions are actively working on drug development to identify molecules with limited adverse effects and robust therapeutic potential.[1]

Global demand for herbal products is growing in the area of diabetes management. Plant-based materials are being meticulously explored for their potential therapeutic applications by leading pharmaceutical companies. Increasingly, herbal medicines are being recognized as safe, side-effect-free alternatives to prescription medications.[2] Approximately 80% of the world's population continues to rely on herbal remedies to address various health conditions. While the *Lepidagathis* genus has been relatively underexplored in scientific experiments pertaining to biological activities, traditional medicines have long utilized plants from this genus to treat a range of ailments, including fever, headache, polyuria, dysentery, skin infections, jungle fever, and urinary tract calculi.[3] Notably, *Lepidagathis pungens* Nees, a member of this genus, has demonstrated potent anticancer and antioxidant potential in previous studies.[4] Therefore, the current research focuses on investigating extractives derived from the powdered

*Author for Correspondence: jothimohanraaj@gmail.com

leaves of *L. pungens* Nees to establish their antidiabetic potential against streptozotocin and nicotinamide (STZ+NIC) induced diabetes in albino rats.

MATERIAL AND METHODS

Materials Used

In this study, all solvents and reagents were analytical grades, purchased from Rankem and Himedia laboratories, Mumbai.

Collection of Plants

A whole plant of *L. pungens* Nees was collected in December from Chennai, Tamil Nadu. Plant specimens were confirmed and authenticated by a certified botanist, and voucher specimens were deposited in the library. In order to grind the plant material into a fine powder, the plant material was shade-dried and subsequently ground using a sieve with a mesh size of 40. Powdered material has been defatted with pet-ether (60–80°C). In a soxhlet apparatus, plant material was extracted successively with methanol and double-distilled water.[5,6] A rotary evaporator was used to evaporate the solutions after they had been filtered separately. As a result, thick extracts were obtained (MELP-28.47% and AELP-24.38%), which were stored for further research.

Acute Toxicity Studies

In accordance with guidelines 423, the Organization for Economic Co-operation and Development (OECD) assessed acute oral toxicity for the extracts. In the experiment, three healthy Wistar rats were used per dose group, comprising both male and female animals. Rats were fasted overnight prior to the experiment. As part of the experimental protocol, the plant extracts and polyherbal formulation were administered orally at doses increasing from 5, 50, 300, and 2000 mg/kg body weight. In addition to behavioral aspects such as alertness, restlessness, and irritability, the animals were closely monitored for a range of parameters. The participants were also continuously monitored for 24 hours for electrical and psychological parameters, including spontaneous activity, reactivity, touch response, pain response, and gait, in addition to autonomic functions like defecation and urination. A further 14 days of observation were conducted after the 24-hour observation period in order to assess the mortality rate of the animals.[7]

Antidiabetic Activity

The experimental animals were classified into seven groups with six animals in each group as shown in Table 1.

As per the protocol, streptozotocin (STZ) at 50 mg/kg body weight was administered intraperitoneally (i.p.) to overnight-fasted rats to induce diabetes. As indicated by the protocol, nicotinamide (NIC) at 120 mg/kg in 0.1 M citrate buffer (pH 4.5) at 0.5 mL/kg body weight was administered as well.[8] A test for diabetes was conducted 48 hours after induction of STZ + NIC in rats, according to the method described.[9] Immediately following the STZ + NIC injection, rats received a 2 mL/kg b.w. solution of 5% glucose w/v (2 mL/kg w/v) to prevent hypoglycemia.

Table 1: Grouping of Animals

Animal group	*Treatment protocol*
I	Normal control
II	Disease control
III	Animal treated with AELP-250 mg/kg
IV	Animal treated with AELP-500 mg/kg
V	Animal treated with MELP-250 mg/kg
VI	Animal treated with MELP-500 mg/kg
VII	Animal treated with glibenclamide-0.25 mg/kg

In this study, rats with fasting blood glucose levels above 200 mg/dl were randomized into six groups based on their fasting blood glucose levels. Over a period of 21 consecutive days, glibenclamide, extracts, and 1% CMC were administered once daily by oral gavage. Glucose levels were measured in a glucometer on the 1st, 7th, 14th, and 21st days of treatment (Table 2). All animals were closely monitored for changes in body weight throughout the experiment.

All experimental animals had their blood samples withdrawn via retroorbital plexus puncture or posterior vena cava, followed by the use of sodium ethylenediaminetetraacetic acid (EDTA) tubes for analysis, as described in 2010.[10] A diethyl ether anesthesia was used to euthanize the animals. The liver and pancreas tissues were subjected to biochemical and pathological analyses. An ice-cold container was used to conduct biochemical analyses, and a 10% formalin solution was used to conduct histopathological analyses.

Estimation of Blood Parameters

The samples were analyzed biochemically using a variety of components. Ortho-Clinical Diagnostics, a division of Johnson and Johnson Company, USA, manufactured One-Touch Horizon glucometers for measuring glucose levels using the whole blood sample. Moreover, the HbA1c level and hemoglobin levels were measured in the whole blood sample. Using a radioimmunoassay kit from Diasorin, Italy, insulin levels were estimated from plasma samples. An enzymatic kit from LAB-KITS was used to measure biochemical markers in serum, the Prietest Easylab - Biochemistry Analyzer from Robonik [India] Pvt Ltd. There were six markers measured in the study: Creatinine, urea, total protein, liver glycogen, total serum cholesterol, and serum triglycerides. The serum glutamate pyruvate transaminase (SGPT) and glutamate oxaloacetate transaminase (SGOT) were also evaluated. Liver tissue homogenates were also used to measure protein and glycogen levels.[11]

Histopathological Examinations

Dehydration of the tissues was carried out using alcohol concentration progressing from 70 to 80, 90%, and absolute alcohol. An automatic tissue processing unit paraffinized the tissues following a 15 to 20-minute xylene cleaning to eliminate residual alcohol and then subjected them to paraffin. Sections were cut from tissue blocks with a thickness of 5 µm using a microtome. A microscope was used to visualize

Table 2: Effect of extracts of *Lepidagathis* on the blood glucose level of diabetes-induced rats

Groups	*Blood glucose level (mg/dL)*			
	0^{th}day	*7^{th}day*	*14^{th}day*	*21^{st}day*
Normal	93.26 ± 1.15	94.12 ± 1.36	96.42 ± 2.94	97.65 ± 2.12
Diabetic	232.35 ± 5.65***[a]	260.88 ± 6.72***[a]	312.95 ± 7.84***[a]	342.23 ± 8.33***[a]
AELP 250 mg/kg	210.85 ± 4.15***[b]	175.32 ± 3.12**[b]	152.17 ± 3.08**[b]	141.76 ± 2.95***[b]
AELP 500 mg/kg	213.28 ± 3.11***[b]	160.32 ± 2.71**[b]	129.86 ± 3.02***[b]	95.44 ± 2.44***[b]
MELP 250 mg/kg	211.65 ± 4.06***[b]	171.87 ± 3.27**[b]	142.74 ± 3.55**[b]	125.62 ± 2.18***[b]
MELP 500 mg/kg	216.42 ± 3.12***[b]	152.38 ± 3.42**[b]	112.63 ± 2.32***[b]	85.29 ± 2.01***[b]
Glibenclamide 0.25 mg/kg	218.45 ± 3.18***[b]	150.57 ± 2.76**[b]	109.78 ± 2.34***[b]	84.82 ± 1.28***[b]

The values were represented as Mean ± SEM (n = 6) *p <0.05, ** p <0.01 and *** p <0.001 were considered significant [a] compared to normal group and [b]compared to the diabetic group. (AELP-Aqueous extract of *Lepidagathis* and MELP-Methanol extract of *Lepidagathis)*

the sections mounted on slides after eosin and hematoxylin staining was performed on them.

Statistics

The values were obtained as mean ± SEM and the differences in means were determined using ANNOVA. The values with p <0.05; p <0.01; p <0.001 were concluded as significant when compared to normal group and diabetic control group using dunnet's test.

RESULTS

When administered as a single oral dose of 2000 mg/kg, the acute toxicity studies revealed no mortality. Consequently, subsequent studies were conducted at lower dose levels, specifically 250 and 500 mg/kg, due to the absence of adverse effects.

Antidiabetic Assay

Effect of L. pungens on the blood glucose levels

The study investigated the potential antidiabetic effects of extracts from *Lepidagathis*, specifically the aqueous extract (AELP) and methanol extract (MELP), in comparison to the standard drug glibenclamide. Blood glucose levels were monitored in albino wistar rats induced with streptozotocin (STZ) and nicotinamide (NIC)-induced diabetes over a 21-day period. On the 0^{th} day, the normal group exhibited a baseline blood glucose level of 93.26 ± 1.15 mg/dL, while the diabetic group showed a significantly elevated level of 232.35 ± 5.65 mg/dL. Throughout the study, the diabetic group consistently displayed elevated blood glucose levels compared to the normal group, confirming the success of the induction. Both doses of AELP (250 and 500 mg/kg) demonstrated a remarkable reduction in blood glucose levels over the experimental period. On the 21^{st} day, AELP at 500 mg/kg exhibited the most significant reduction, with a blood glucose level of 95.44 ± 2.44 mg/dL, highlighting its potential as an antidiabetic agent. Similar to AELP, both concentrations of MELP (250 and 500 mg/kg) exhibited significant antidiabetic effects. MELP at 500 mg/kg demonstrated a notable reduction in blood glucose levels on the 21^{st} day, recording 85.29 ± 2.01 mg/dL (Table 2). Both AELP and MELP demonstrated promising antidiabetic potential, comparable to the standard drug glibenclamide, emphasizing their significance as potential therapeutic agents for the treatment of diabetes (Figure 1).

*Effect of **L. pungens** on the changes of body weight*

The investigation into the effect of *Lepidagathis* extracts on body weight changes revealed significant values. In the normal group, rats exhibited a steady increase in body weight from an initial 186.36 ± 5.18 gm to a final 198.46 ± 5.27 gm, indicating healthy growth over the experimental period. In contrast, diabetic rats showed a notable decrease in body weight, starting at 192.18 ± 4.28 gm and concluding at 169.43 ± 3.21 gm, reflecting a significant reduction of -18.55 ± 3.67 gm. Upon administration of AELP at both 250 and 500mg/kg, there was a distinct impact on body weight changes. The AELP 250 mg/kg group exhibited a slight reduction in body weight (-1.34 ± 1.48 gm), while the AELP 500 mg/kg group displayed a modest increase (2.88 ± 2.15 gm). Similarly, the MELP groups at 250 and 500 mg/kg demonstrated positive effects on body weight changes. The MELP 250 mg/kg group displayed an increase of 4.16 ± 1.43 gm, and the MELP 500 mg/kg group showed a comparable rise of 4.28 ± 1.08 gm (Table 3 and Figure 2). These findings highlight the potential of both AELP and MELP, along with the standard drug glibenclamide, to influence positive body weight changes in diabetes-induced rats.

Effect of L. pungens on the insulin and hemoglobin

The extracts, AELP and MELP, demonstrated superior activity compared to the standard drug glibenclamide, as displayed in

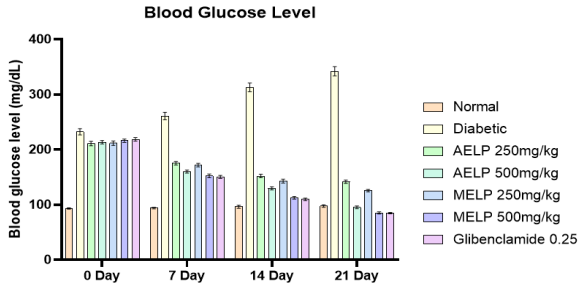


Figure 1: Effect of extracts of *Lepidagathis* on the blood glucose level of diabetes-induced rats

Table 3: Effect of extracts of *Lepidagathis* on the body weight changes of diabetes-induced rats

Groups	*Body weight (gm)*		*Change in body weight (gm)*
	Initial	*Final*	
Normal	186.36 ± 5.18	198.46 ± 5.27	11.97 ± 1.36
Diabetic	192.18 ± 4.28	169.43 ± 3.21	-18.55 ± 3.67***[a]
AELP 250 mg/kg	201.57 ± 5.99	200.54 ± 4.09	-1.34 ± 1.48***[b]
AELP 500 mg/kg	197.65 ± 4.27	199.24 ± 5.12	2.88 ± 2.15***[b]
MELP 250 mg/kg	192.35 ± 4.31	196.54 ± 4.82	4.16 ± 1.43***[b]
MELP 500 mg/kg	199.87 ± 5.94	203.21 ± 4.39	4.28 ± 1.08***[b]
Glibenclamide 0.25 mg/kg	196.55 ± 4.82	199.55 ± 3.17	3.65 ± 1.11***[b]

The values were represented as Mean ± SEM (n = 6). * p <0.05, ** p <0.01 and *** p <0.001 were considered significant [a] compared to normal group and [b]compared to the diabetic group.

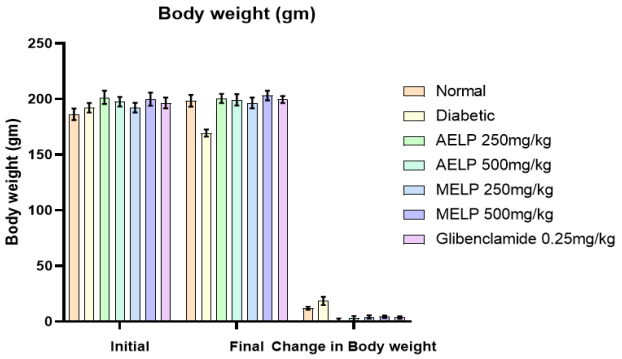


Figure: 2 Effect of Extract of *Lepidagathis* on the body weight changes of diabetes-induced animals

Table 4 and Figure 3. Notably, both AELP and MELP exhibited a significant improvement in plasma insulin levels (AELP 500 mg/kg: 18.96 ± 1.18 µIU/mL, MELP 500 mg/kg: 20.71 ± 1.68 µIU/mL) and a substantial reduction in HbA1C (AELP 500 mg/kg: 0.42 ± 0.04b, MELP 500 mg/kg: 0.33 ± 0.4) compared to the diabetic group. These effects were either comparable to or even more pronounced than those observed with the standard drug (21.41 ± 1.97 µIU/mL and 0.36 ± 0.05).

Effect of L. pungens on the serum biochemical profile

Table 5 and Figure 4 summarize the impact of the AELP, MELP, and the standard drug glibenclamide on liver glycogen, total protein, urea, creatinine, and SGOT levels in diabetes-induced rats. In comparison to the diabetic group, which exhibited significantly reduced liver glycogen levels (2.31 ± 0.42 g/100 mg tissue), both AELP and MELP demonstrated notable improvements. AELP at 500 mg/kg displayed a substantial increase (5.61 ± 0.44 g/100 mg tissue), surpassing even the normal group. Similar trends were observed in total

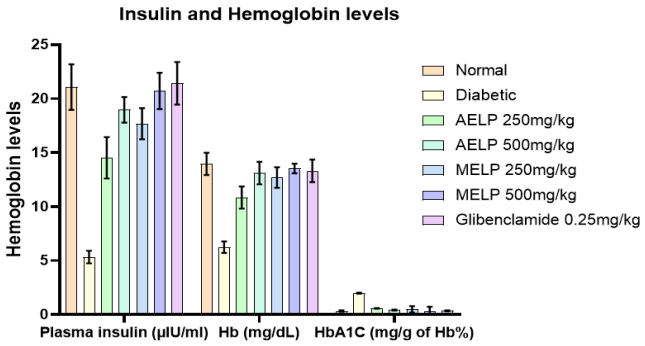


Figure 3: Effect of extracts of *Lepidagathis* on the insulin and hemoglobin levels of diabetes-induced rats

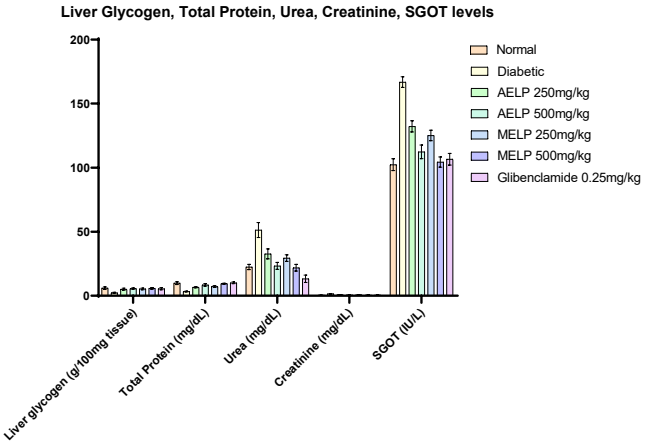


Figure: 4 Effect of extracts of *Lepidagathis* on the liver glycogen, total protein, urea, creatinine, SGOT levels of diabetes-induced rats

protein levels, where the diabetic group showed a decrease (3.32 ± 0.29 mg/dL), while AELP and MELP exhibited significant improvements. AELP at 500 mg/kg recorded the highest total protein levels (8.41 ± 0.94 mg/dL).

Urea levels, elevated in the diabetic group (51.27 ± 5.87 mg/dL), were significantly reduced by both AELP and MELP. Notably, AELP at 500 mg/kg (23.29 ± 2.71 mg/dL) showcased a substantial decrease, comparable to the normal group. Creatinine levels, elevated in the diabetic group (1.46 ± 0.03 mg/dL), were effectively mitigated by AELP and MELP. AELP at 500 mg/kg exhibited the most significant reduction (0.55 ± 0.07 mg/dL). SGOT levels increased in the diabetic group (166.74 ± 4.13 IU/L), were significantly lowered by both AELP and MELP. AELP at 500 mg/kg (112.31 ± 5.34 IU/L) and glibenclamide (106.55 ± 4.55 IU/L) demonstrated notable reductions.

Effect of L. pungens on the lipid profile

Table 6 illustrates the impact of AELP, MELP, and the standard drug glibenclamide on lipid levels in diabetes-induced animals. In comparison to the diabetic group, which exhibited markedly elevated triglycerides (TG: 210.86 ± 9.96 mg/dL), total cholesterol (TC: 132.49 ± 6.55 mg/dL), and low-density lipoprotein (LDL: 148.06 ± 7.51 mg/dL), along with reduced

Table 4: Effect of extracts of *Lepidagathis* on the insulin and hemoglobin levels of diabetes-induced rats

Groups	*Plasma insulin (µIU/mL)*	*Hb (mg/dL)*	*HbA1C (mg/g of Hb%)*
Normal	21.06 ± 2.11	13.96 ± 1.03	0.34 ± 0.06
Diabetic	5.33 ± 0.58***[a]	6.24 ± 0.53***[a]	1.99 ± 0.05***[a]
AELP 250mg/kg	14.52 ± 1.91**[b]	10.84 ± 1.02**[b]	0.58 ± 0.03***[b]
AELP 500mg/kg	18.96 ± 1.18***[b]	13.11 ± 1.04***[b]	0.42 ± 0.04***[b]
MELP 250mg/kg	17.68 ± 1.44***[b]	12.69 ± 0.95***[b]	0.49 ± 0.3***[b]
MELP 500mg/kg	20.71 ± 1.68***[b]	13.53 ± 0.44***[b]	0.33 ± 0.4***[b]
Glibenclamide 0.25mg/kg	21.41 ± 1.97***[b]	13.31 ± 1.05***[b]	0.36 ± 0.05***[b]

The values were represented as Mean ± SEM (n = 6). *p <0.05, ** p <0.01 and *** p <0.001 were considered significant [a] compared to normal group and [b]compared to the diabetic group. AELP-Aqueous extract of *Lepidagathis* and MELP-Methanol extract of *Lepidagathis*

Table 5: Effect of extracts of *Lepidagathis* on the liver glycogen, total protein, urea, creatinine, SGOT levels of diabetes-induced rats

Groups	*Liver glycogen (g/100 mg tissue)*	*Total protein (mg/dL)*	*Urea (mg/dL)*	*Creatinine (mg/dL)*	*SGOT (IU/L)*
Normal	5.99 ± 0.88	9.85 ± 1.07	22.43 ± 2.07	0.41 ± 0.05	102.31 ± 4.56
Diabetic	2.31 ± 0.42***[a]	3.32 ± 0.29***[a]	51.27 ± 5.87***[a]	1.46 ± 0.03***[a]	166.74 ± 4.13***[a]
AELP 250 mg/kg	5.09 ± 0.79***[b]	6.64 ± 0.43***[b]	32.66 ± 3.89*[b]	0.72 ± 0.04**[b]	132.19 ± 4.34*[b]
AELP 500 mg/kg	5.61 ± 0.44***[b]	8.41 ± 0.94***[b]	23.29 ± 2.71***[b]	0.55 ± 0.07***[b]	112.31 ± 5.34***[b]
MELP 250 mg/kg	5.35 ± 0.65***[b]	7.23 ± 0.71***[b]	29.41 ± 2.57**[b]	0.66 ± 0.05***[b]	125.08 ± 4.09**[b]
MELP 500 mg/kg	5.82 ± 0.62***[b]	9.44 ± 0.34***[b]	21.86 ± 2.61***[b]	0.51 ± 0.06***[b]	104.34 ± 3.97***[b]
Glibenclamide 0.25 mg/kg	5.47 ± 0.77***[b]	10.11 ± 0.66***[b]	13.23 ± 2.85***[b]	0.48 ± 0.04***[b]	106.55 ± 4.55***[b]

The values were represented as Mean ± SEM (n = 6). * p <0.05, ** p <0.01 and *** p <0.001 were considered significant [a] compared to normal group and [b]compared to the diabetic group. AELP-Aqueous extract of *Lepidagathis* and MELP-Methanol extract of *Lepidagathis*

high-density lipoprotein (HDL: 19.87 ± 1.02 mg/dL), both AELP and MELP demonstrated significant improvements. AELP at 500 mg/kg displayed substantial reductions in TG (81.12 ± 4.3 mg/dL), TC (95.66 ± 3.48 mg/dL), and LDL (37.44 ± 4.12 mg/dL) levels, along with an increase in HDL (29.55 ± 1.25 mg/dL), outperforming the diabetic group. MELP at 500 mg/kg also showcased positive effects, particularly in TG (71.17 ± 5.83 mg/dL) and HDL (30.05 ± 1.54 mg/dL), comparing favorably with glibenclamide (TG: 70.67 ± 4.88 mg/dL, HDL: 31.25 ± 1.74 mg/dL). These results highlight the potential of AELP and MELP in modulating lipid levels, suggesting their therapeutic significance in mitigating dyslipidemia associated with diabetes (Figure 5).

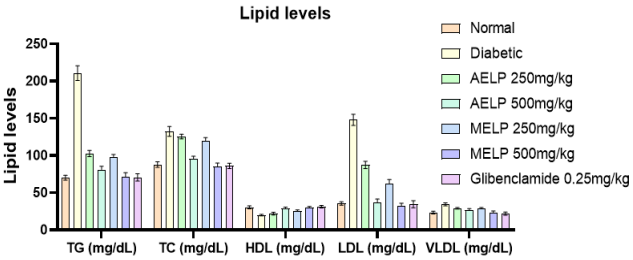


Figure: 5 Effect of extracts of *Lepidagathis* on the lipid levels of diabetes-induced rats

Effect of L. pungens on the antioxidant profile

In Table 7 and Figure 6, the impact of aqueous extract of *Lepidagathis* (AELP), methanol extract of *Lepidagathis* (MELP), and the standard drug glibenclamide on antioxidant enzyme levels in diabetes-induced rats. In contrast to the diabetic group, which exhibited elevated SOD, CAT, and GPx, along with increased lipid peroxidation (LOP), both AELP and MELP demonstrated significant improvements. AELP at 500 mg/kg displayed notable increases in SOD (5.34 ± 0.83 UI/mg protein) and GP (21.35 ± 2.14 UI/mg protein) levels. Additionally, AELP at both 250 and 500 mg/kg showed considerable reductions in LPO (18.72 ± 1.46 UI/mg protein and 25.48 ± 1.38 UI/mg protein, respectively), indicating enhanced antioxidant activity. Similarly, MELP at 500 mg/kg exhibited significant enhancements in SOD (5.01 ± 0.99 UI/mg protein), CAT (2.18 ± 0.31 UI/mg protein), and GP (23.14 ± 1.97 UI/mg protein) levels, along with a substantial reduction in LPO (27.55 ± 1.09 UI/mg protein), highlighting its antioxidant potential in counteracting oxidative stress significantly (p <0.001) better than standard group. These results collectively underscore the antioxidative potential of AELP and MELP, comparable to the standard drug glibenclamide, in mitigating oxidative stress in drugs-induced animals.

Histopathological Examination

The histopathological analysis of liver tissue from rats induced with STZ-NIC-induced diabetes revealed clear pathological changes, including hepatocellular necrosis, vacuolation, and inflammatory infiltrates, indicative of diabetic hepatopathy (Figures 7 & 8). This pronounced degeneration underscored the

Table 6: Effect of extracts of *Lepidagathis* on the lipid levels of diabetes-induced rats

Groups	*Lipid levels (mg/dL)*				
	TG	*TC*	*HDL*	*LDL*	*VLDL*
Normal	70.24 ± 3.22	87.78 ± 3.72	30.44 ± 1.91	35.65 ± 2.12	23.42 ± 1.95
Diabetic	210.86 ± 9.96***[a]	132.49 ± 6.55***[a]	19.87 ± 1.02***[a]	148.06 ± 7.51***[a]	34.37 ± 1.88***[a]
AELP 250 mg/kg	102.71 ± 4.28**[b]	125.47 ± 3.11**[b]	22.07 ± 1.88*[b]	87.55 ± 4.94*[b]	29.05 ± 1.04**[b]
AELP 500 mg/kg	81.12 ± 4.3***[b]	95.66 ± 3.48***[b]	29.55 ± 1.25***[b]	37.44 ± 4.12***[b]	26.55 ± 2.14***[b]
MELP 250 mg/kg	98.43 ± 3.09**[b]	120.06 ± 4.12**[b]	25.71 ± 1.23**[b]	62.46 ± 5.31**[b]	28.48 ± 1.56**[b]
MELP 500 mg/kg	71.17 ± 5.83***[b]	85.14 ± 4.72***[b]	30.05 ± 1.54***[b]	32.29 ± 3.63***[b]	23.42 ± 2.04***[b]
Glibenclamide 0.25 mg/kg	70.67 ± 4.88***[b]	86.06 ± 3.71***[b]	31.25 ± 1.74***[b]	34.67 ± 4.86***[b]	22.01 ± 2.03***[b]

The values were represented as Mean ± SEM (n = 6). * p <0.05, ** p <0.01 and *** p <0.001 were considered significant [a] compared to the normal group and [b]compared to the diabetic group. AELP-Aqueous extract of *Lepidagathis* and MELP-Methanol extract of *Lepidagathis*

Table 7: Effect of extracts of *Lepidagathis* on the antioxidant enzyme levels of diabetes-induced rats

Groups (UI/mg protein)	*SOD*	*CAT*	*GP*	*GR*	*LPO*
Normal	5.81 ± 0.54	2.25 ± 0.43	24.71 ± 2.14	32.75 ± 2.28	26.26 ± 1.17
Diabetic	14.29 ± 1.08***[a]	7.88 ± 0.85***[a]	17.32 ± 1.86***[a]	8.71 ± 1.04***[a]	15.08 ± 1.97***[a]
AELP 250 mg/kg	7.88 ± 0.86***[b]	4.77 ± 0.4***[b]	20.55 ± 2.03***[b]	20.99 ± 3.87***[b]	18.72 ± 1.46*[b]
AELP 500 mg/kg	5.34 ± 0.83***[b]	3.93 ± 0.33***[b]	21.35 ± 2.14***[b]	33.45 ± 3.99***[b]	25.48 ± 1.38***[b]
MELP 250 mg/kg	6.95 ± 0.76***[b]	4.64 ± 0.47***[b]	20.35 ± 2.05***[b]	23.36 ± 2.09***[b]	20.05 ± 1.61**[b]
MELP 500 mg/kg	5.01 ± 0.99***[b]	2.18 ± 0.31***[b]	23.14 ± 1.97***[b]	34.31 ± 2.38***[b]	27.55 ± 1.09***[b]
Glibenclamide 0.25 mg/kg	6.53 ± 1.01***[b]	3.99 ± 0.26***[b]	22.86 ± 1.74***[b]	29.07 ± 2.57***[b]	24.38 ± 1.55***[b]

The values were represented as Mean ± SEM (n = 6). * p <0.05, ** p <0.01 and *** p <0.001 were considered significant [a] compared to normal group and [b]compared to the diabetic group. AELP-Aqueous extract of *Lepidagathis* and MELP-Methanol extract of *Lepidagathis*

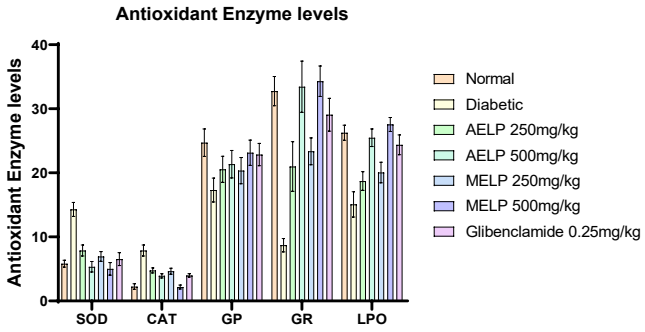


Figure 6: Effect of extracts of *Lepidagathis* on the antioxidant enzyme levels of diabetes-induced rats

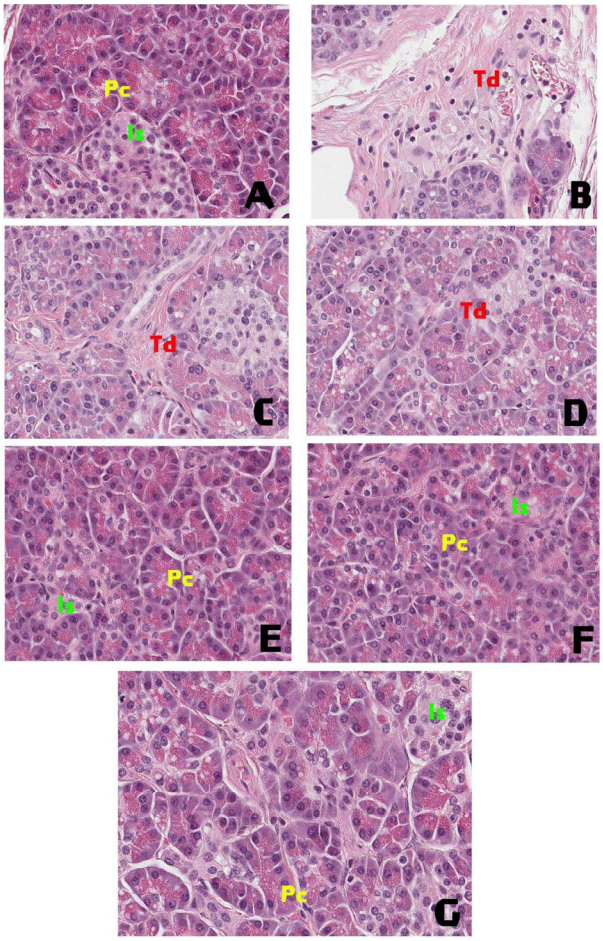
degenerative impact of the STZ on liver morphology. However, the administration of AELP and MELP, particularly at higher concentrations, exhibited a significant protective effect on liver cells. At 500 mg/kg, both AELP and MELP demonstrated a significant reduction in hepatocellular degeneration, preserving the normal hepatic architecture. Moreover, a decrease in inflammatory infiltrates suggested an anti-inflammatory effect, further contributing to the observed hepatoprotection. Importantly, these protective trends were notably comparable to the effects observed with the standard drug glibenclamide, affirming the hepatoprotective potential of both AELP and MELP.

Examination of pancreas tissue from diabetic rats revealed characteristic changes associated with diabetic pancreatitis, including degeneration of islet cells, reduced beta-cell mass and disrupted tissue architecture. In contrast, treatment with AELP and MELP demonstrated substantial protective effects on pancreatic tissue. AELP at 500 mg/kg and MELP at 500 mg/kg exhibited a pronounced preservation of islet cell architecture, an increase in beta-cell mass, and a reduction in inflammatory changes within the pancreas. These findings strongly indicated the potential of AELP and MELP to counteract diabetes-induced damage in pancreatic tissues. Notably, the protective effects observed were on par with those elicited by the standard drug glibenclamide, highlighting the comparable efficacy of both extracts in ameliorating pancreatic degeneration.

DISCUSSION

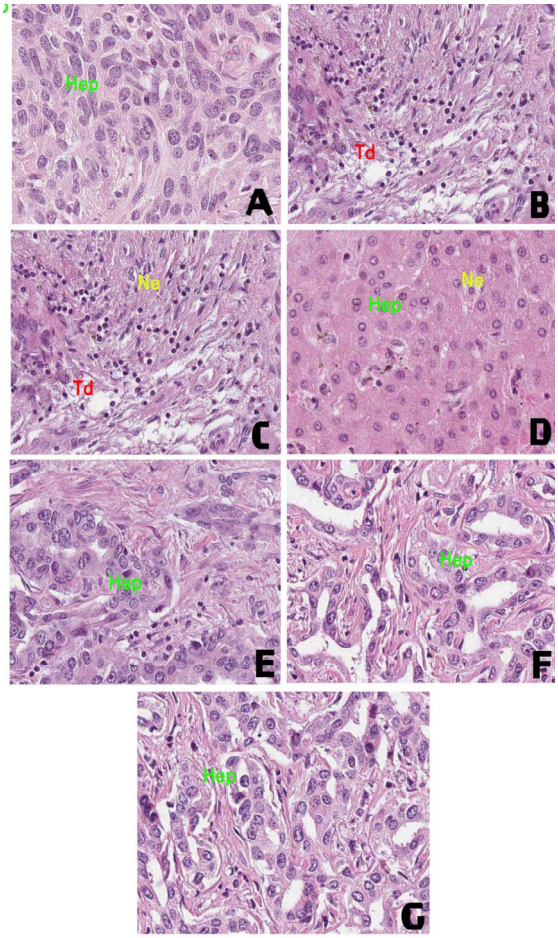
The dynamics of diabetes are rapidly changing in low- and middle-income countries, where diabetes affects almost 6% of the global population.[12] Various plant species have been documented in traditional systems of medicine to be helpful in treating endocrine disorders, such as diabetes. There was substantial literature claiming that herbal drugs are synergistic, potentiative, and agonistic/antagonistic, as well as exhibiting less side effects than synthetic drugs, which have been used for disease treatment and prevention for decades.[13]

The current investigation aimed to assess the potential therapeutic effects of AELP and MELP in preventing STZ+NIC diabetes-induced complications in albino Wistar rats. This comprehensive study showcased various physiological parameters, including blood glucose levels, body weight



A. Control; B. Diabetic; C. AELP 250 mg/kg; D. MELP 250 mg/kg; E. AELP 500 mg/kg; F. MELP 500 mg/kg; (G. standard; Td-Tissue degeneration; Pc- Pancreatic cell; Is-Pancreatic Islet cells)

Figure: 7 Effect of extracts on the histopathology of the pancreas



A.Control; B. Diabetic; C. AELP 250 mg/kg; D. MELP 250 mg/kg; E. AELP 500 mg/kg; F. MELP 500 mg/kg; (G. standard; Hep-hepatocyte; Ne-Neutrophils; Td- Tissue degeneration)

Figure: 8 Effect of extracts on the histopathology of liver tissue

changes, insulin resistance, lipid profiles, liver function markers, antioxidant enzyme levels, and histopathological alterations in liver and pancreas tissues. The results demonstrated that both AELP and MELP, particularly at higher doses 500 mg/kg, exhibited significant protective effects against diabetes-induced alterations. Significant improvements were observed in blood glucose levels, body weight changes, insulin sensitivity, lipid profiles, and antioxidant enzyme levels. Histopathological examinations revealed marked protection against degeneration in liver and pancreas tissues, showcasing the potential of these extracts in controlling the complications associated with diabetes.

STZ and NIC are commonly employed to induce diabetes in experimental models. STZ, a naturally occurring glucosamine-nitrosourea compound, selectively damages pancreatic beta cells, leading to insulin deficiency.[14] Meanwhile, NIC serves to protect beta cells from the toxic effects of STZ and enhances its diabetogenic action, converting the induced diabetes from insulin-dependent to insulin non-dependant.[15] Together, STZ and NIC induce a diabetic state by disrupting glucose metabolism insulin secretion, and promoting oxidative stress. The observed alterations in the experimental group, induced by STZ/NIC, reflected the multifaceted impact of these agents on glucose homeostasis, insulin signaling, and oxidative stress pathways, thereby replicating key aspects of diabetes pathophysiology.[16]

The protective effects exhibited by AELP and MELP in this study may be attributed to their diverse bioactive compounds. The extracts demonstrated a significant reduction in blood glucose levels, indicative of potential anti-hyperglycemic activity. Additionally, the extracts mitigated oxidative stress, as evidenced by improvements in antioxidant enzyme levels. These effects point towards potential mechanisms of action, including enhanced insulin sensitivity, preservation of beta-cell mass, and antioxidant defense.

AELP and MELP may influence glucose metabolism by modulating insulin signaling pathways, facilitating glucose uptake, and preserving beta-cell function. The antioxidant properties observed could be attributed to the presence of bioactive compounds that scavenge reactive oxygen species

(ROS), mitigating oxidative stress—an integral component of diabetes-induced tissue damage. To delineate the specific compounds contributing to the observed activities, a literature review was conducted. *Lepidagathis*, the source plant, is known for its diverse phytochemical profile. Previous studies on *Lepidagathis* extracts have identified flavonoids, alkaloids, tannins, and phenolic compounds, among others. These constituents are recognized for their antioxidant, anti-inflammatory, and hypoglycemic properties.[17]

Comparisons with previous studies are essential for contextualizing and validating our findings. A study suggested the effects of *Lepidagathis* species on diabetes and antioxidant activities.[18] Our study aligns with these findings, strengthening the evidence for the antidiabetic and antioxidative potential of *Lepidagathis* extracts.

However, variations in study designs, extract preparation methods, and animal models must be considered when drawing comparisons. Despite these differences, the consistent outcomes across studies reinforce the credibility of AELP and MELP as potential agents in diabetes management.

CONCLUSION

While this study provides valuable insights, future research endeavors could elucidate the molecular mechanisms underlying the observed effects. Exploring the specific bioactive compounds within AELP and MELP responsible for their therapeutic actions could pave the way for targeted drug development. Additionally, investigating the long-term effects and potential side effects would contribute to a comprehensive understanding of the safety profile of these extracts. Furthermore, exploring the potential synergistic effects of AELP and MELP with conventional antidiabetic drugs or other natural compounds could offer novel therapeutic combinations. *In-vivo* studies with a larger sample size and diverse experimental conditions would enhance the reproducibility and inference of these findings to humans. Finally, this study lays the foundation for future investigations that may assist in developing effective and innovative diabetes management strategies.

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