EVALUATION OF ANTI-HYPERGLYCEMIC ACTIVITY OF ETHANOLIC EXTRACT OF AERIAL PARTS OF *LUFFA ACUTANGULA* AGAINST STREPTOZOTOCIN-NICOTINAMIDE INDUCED TYPE II DIABETIC RATS

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Abstract

Luffa acutangula is a species of Luffa. It is also known as the ridge gourd, angled gourd. Previous proven activities based on literature review show that some plant parts have anti-diabetic properties, The ability of plant aerial parts to prevent diabetes, however, has not been proved scientifically. The current study's objective was to evaluate the anti-hyperglycemic efficacy of an ethanolic extract of *Luffa acutangula* aerial parts (EELA) in type II diabetic rats that had been induced by streptozotocin and nicotinamide. After 15 minutes of NIC (120 mg/kg *i.p.*) treatment, type 2 diabetes was established by administering STZ (60 mg/kg, *i.p.*). Diabetic rats received EELA (400 and 800 mg/kg, *p.o.*, respectively) for 28 days. Blood glucose, SGPT, SGOT, blood urea, creatinine, haemoglobin, total cholesterol, triglycerides, LPO, and GPX levels were all considerably reduced in diabetic rats who received EELA treatment. Nevertheless, EELA-treated diabetic rats exhibited body weight, HbA1c, CAT, SOD, GSH, hexokinase, liver glycogen, and G6P that were considerably greater. Histopathological studies have demonstrated that treatment groups experienced pancreatic beta cell regeneration. By using GC-MS analysis, it is proven that EELA contains Phenol, Phytol, Maleic anhydride, Neophytadiene, Furan, Lutein, and Eugenol. According to the results of the current investigation, EELA may be effective in treating Diabetes mellitus without producing any overt harmful effects. The anti-diabetic effects of EELA were comparable to those of the common medication Glibenclamide. The laboratory results from this investigation support the conventional usage of EELA to treat diabetes, indicating a need to isolate and assess active ingredients responsible for the demonstrated biological activity for the upcoming studies.

Keywords: Streptozotocin, Glibenclamide, Antioxidant activity, *Luffa acutangula*, Furan, Lutein.

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1. Introduction

A sustained increase in blood glucose levels is the hallmark of diabetes mellitus [1]. Frequent urination, increased thirst, and increased appetite are the main symptoms. Untreated diabetes will result in acute diabetic ketoacidosis (DKA). In the long run, it results in nerve damage, cognitive decline, foot ulcers, chronic renal disease, cardiovascular disease, and stroke [2][3]. People with Type 1 diabetes receive insulin injections to help them manage their illness. For the management of Type II diabetes, it is advised to follow a healthy diet, engage in regular physical exercise, abstain from tobacco use, monitor blood pressure, take care of your feet and eyes, and use medications such antihyperglycemic drugs [4][5].

Based on a review of the literature, prior studies on Luffa acutangula have shown that it has CNS depressant, antibacterial, analgesic and anti-inflammatory, antihyperlipidemic, antidiabetic, hepatoprotective, anticancer, antihyperlipidemic, and antihyperlipidemic in fruit activity. activity that modulates immunity in the apple pericarp. Fruit pulp extract from dried fruit has antiulcer effects. action against microorganisms in aerial parts. The leaves also have antibacterial and anti-inflammatory qualities in addition to analgesic effects. The seed has narcotic and anti-inflammatory properties, and the root has antibacterial properties [6][7][8].

2. Materials and Methods

a) Plant material and extraction:

The Botanical Survey of India, Southern Regional Centre, Coimbatore - 641003 certified the *Luffa acutangula* aerial pieces that were obtained in Kalapatti, Coimbatore district (11.086146°N, 77.036297°E). Plant authentication certificate number: BSI/SRC/5/23/2021/Tech.

The plant components were mechanically ground, air dried, and sieved with 40 and 60 mesh diameters. 280 g of the powdered aerial component of the plant was mixed for 72 hours with 60°C petroleum ether for defatting and 99 % ethanol for extraction using the hot continuous extraction method and Soxhlet apparatus [9][10]. After being heated for 30 minutes, the collected components were purified 72 hours later. Extract yield is 7.75% (w/w) when stored between 2 and 8°C [8].

b) Experimental animals:

To examine acute toxicity and evaluate anti-diabetic effectiveness, male Sprague Dawley rats (150-200 g) were utilized. All animals were kept under typical laboratory conditions, which included a temperature (22±2°C) and a humidity (45±5) % with a 12-hour day/12-hour night cycle.

The animals were fed a typical laboratory libitum and were free to drink as much water as they wanted. The research was completed with the consent of the Institutional Animal Ethics Committee and in accordance with the institutional ethical standards for the care of laboratory animals at the KMCH College of Pharmacy (Approval no. KMCRET/ MPharm/14/ 2021)

c) Diabetes experimentation in rats:

After overnight starvation, STZ was dissolved in freshly prepared 0.1 M cold citrate buffer (pH 4.5) and administered to rats through intraperitoneal injection (60 mg/kg). Rats were given a 5 percent dextrose solution for the following 24 hours following STZ injection in order to stop the deadly hypoglycemia that STZ causes due to increased pancreatic insulin release after its treatment.

After 15 minutes, NIC was delivered intraperitoneally (120 mg/kg) prepared in normal saline for partial pancreatic protection. Diabetes was confirmed 72h after induction by measurement of tail vein blood glucose levels using glucose meter (Accu-Chek® Active blood glucose meter, Roche Diabetes Care, Inc., Indiana).

Diabetic rats were housed in conventional laboratory conditions for one week to allow blood glucose levels to stabilise. After 3 days of diabetes induction, blood glucose levels were measured again, and animals with blood glucose levels more than 200 mg/dL were chosen for the study [11].

d) Experimental design for antidiabetic activity:

According to Figure1 animal experiment was done.

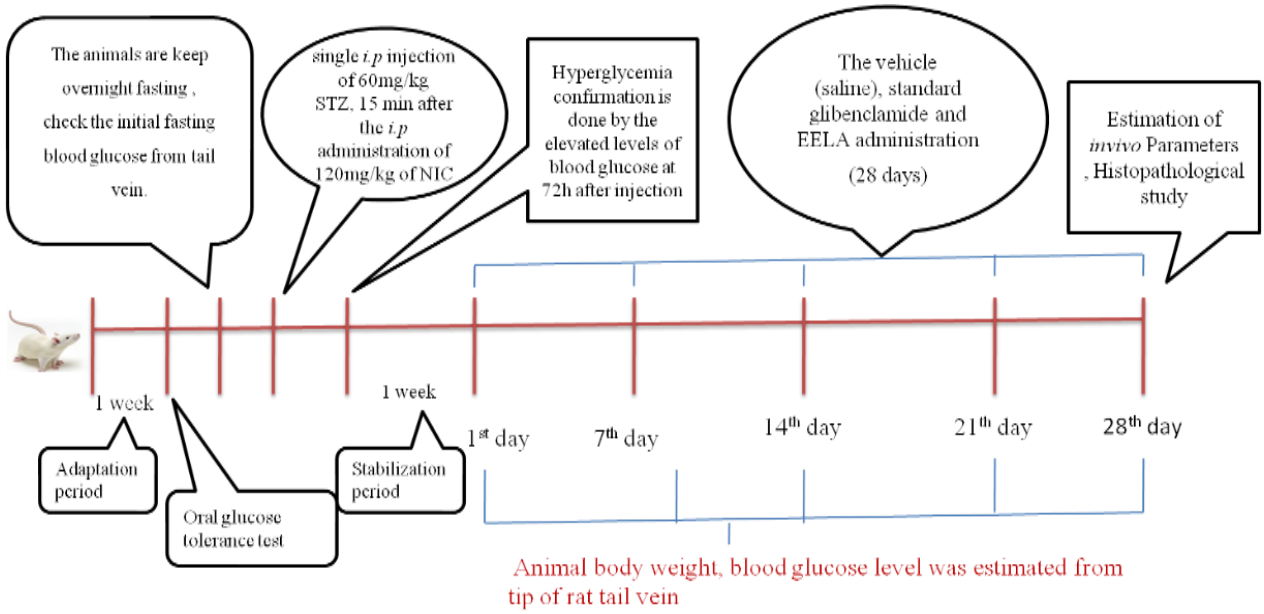


Figure 1: Experimental animal study design

e) Estimation of biochemical parameters:
Commercially available kits were used to estimate Hb and HbA1c [12]. Commercial kits were used to determine blood lipid profiles such as total cholesterol (TC) [13] and triglycerides (TG) [14]. Commercial kits were used to measure SGPT, SGOT, creatinine, urea [15]. Semi autoanalyzer (Photometer 5010V5+, Germany) was used to calculate all the biochemical parameters listed above.

f) Determination of antioxidant levels:
After scarification, the liver of all group animals was collected and cleaned with ice cold saline to eliminate blood. In the liver, antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), reduced glutathione (GSH), and lipid peroxidation were measured[16][17].

Determination of Total protein, Liver glycogen, Carbohydrate metabolizing enzymes:
After scarification, all group animals' liver were removed and cleaned with ice cold saline to eliminate blood. In the liver, total protein, liver glycogen, and carbohydrate metabolising enzymes [11][18] such as Hexokinase and Glucose-6-phosphatase were measured.

Histological examinations:
The pancreas of all rats was dissected for histopathological study at the end of the experiment (after 28 days of treatment with respective groups). Histopathological alterations were seen using the haematoxylin–eosin (H&E) stain [19][17].

Statistical analysis:
All data represented as mean SEM were subjected to one-way analysis of variance (ANOVA), which was followed by Dunnett's test for multiple comparisons using prism Graph pad version 9.0 and P values.

3. Results

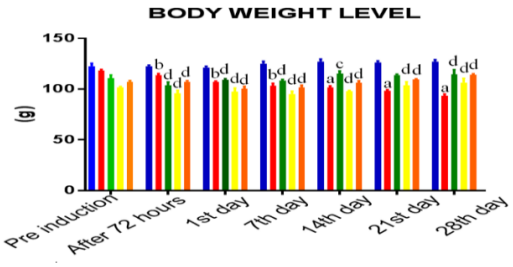
Acute toxicity study:
Rats given EELA orally at a dosage of 2000 mg/kg for 14 days experienced no negative side effects, and no animals perished. It was found that rats were unaffected by EELA up to a dose of 2000 mg/kg per body weight. In order to investigate the hypoglycemic effect, dose levels of 400 and 800 mg/kg were employed.

Effect of EELA on blood glucose and body weight:
When diabetic rats received STZ, their body weight significantly decreased in comparison to the rats in the normal control group (Table 1, Figure 2).

Table 1: Effect of EELA on blood weight

Groups	Before induction	After 72h induction	1st day of treatment	7th day of treatment	14th day of treatment	21st day of treatment	28th day of treatment
Control	122.50±2.88	122.50±1.04	121.33±1.21	125.00±2.44	127.00±2.64	126.33±1.52	127.00±2.00
(STZ+NIC)	118±1.41	113.5±1.87$^{\#\#}$	107.16±0.75$^{\#\#}$	109.00±1.26$^{\#\#}$	101.66±1.50$^{\#\#\#}$	98.16±1.32$^{\#\#\#}$	93.33±1.86$^{\#\#\#}$
(STZ+NIC) + STD (20mg/kg)	110.66±3.26	103.83±3.06***	109.0±1.26***	97.5±3.50***	115.20±2.58**	113.8±0.83**	114.5±4.64**
(STZ+NIC) + EELA (400mg/kg)	101.83±0.75	95.83±2.99***	97.50±3.50***	95.20±2.77***	97.80±0.83***	103.75±3.40***	106.25±4.34**
(STZ+NIC) + EELA (800mg/kg)	107.00± 1.41	107.16±1.16***	100.33±2.50***	101.60±2.30***	106.00±2.16***	109.25±0.95***	114.00±1.15***

Values are expressed as mean ±SEM, n=6, one way ANOVA followed by Dunnett's multiple comparisons test, ns-non significant, Compared with normal control; $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001, Compared with disease control; *p<0.05, **p<0.01, ***p<0.001.



[a]: p<0.001 diabetic control compared with normal control groups; [b]:p<0.01 diabetic control compared with normal control groups; [c]: p<0.01 EELA 100,200 mg/kg and Glibenclamide 20mg/kg compared with disease control groups; [d]: p<0.001 EELA 100,200 mg/kg and Glibenclamide 20mg/kg compared with disease control groups; ns-non significant.

Figure 2: Body weight analysis graphical representation

Table 2: Effect of EELA on blood glucose

Groups	Before induction	After 72h induction	1st day of treatment	7th day of treatment	14th day of treatment	21st day of treatment	28th day of treatment
Control	71.50±1.87	75.00±0.89	76.60±1.14	76.40±1.67	76.33±2.51	77.66±1.52	77.33±2.08
(STZ+NIC)	77.16±1.72	353.50±2.16$^{\#\#\#}$	365.16±3.125$^{\#\#\#}$	320.50±1.04$^{\#\#\#}$	376.66±1.75$^{\#\#\#}$	397.66±1.50$^{\#\#\#}$	395.00±3.52$^{\#\#\#}$
(STZ+NIC) + STD (20mg/kg)	77.50±1.51	356.66±1.36^{ns}	320.50±1.04***	327.33±1.36*	202.60±1.81***	155.50±1.29***	107.25±1.70***
(STZ+NIC) + EELA (400mg/kg)	75.00±3.22	355.5±1.04^{ns}	327.33±1.36***	254.5±1.04***	256.40±1.41***	188.00±1.41***	128.25±1.70***
(STZ+NIC) + EELA (800mg/kg)	76.50±2.73	355.66±2.16^{ns}	322.50±0.83***	232.60±2.07***	224.75±0.95***	177.50±2.64***	117.25±2.06***

Values are expressed as mean ±SEM, n=6, one way ANOVA followed by Dunnett's multiple comparisons test, ns-non significant, Compared with normal control; $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001,Compared with disease control; *p<0.05, **p<0.01, ***p<0.001.

Effect of EELA on Hb, HbA1c levels:

Induction of diabetes considerably increased HbA1c levels but decreased Hb levels in comparison to normal control rats. Treatment with EELA 400 and 800 mg/kg dosages and glibenclamide significantly (P0.001 and P0.01) decreased high HbA1c levels and elevated Hb levels to normal levels when compared to disease control rats (Table 3). However, it was discovered that EELA 800 mg/kg was more efficacious than EELA 400 mg/kg in diabetic rats.

Table 3: Effect of EELA on Haematological parameters

Parameters	Control	(STZ+NIC)	(STZ+NIC)+ STD(20mg/kg)	(STZ+NIC)+ EELA(400mg/kg)	(STZ+NIC)+ EELA(800mg/kg)
Haemoglobin (g/dL)	16.20±0.82	8.62±0.37$^{\#\#\#}$	14.16±0.24***	10.99±1.07*	11.50±1.27**
Glycosylated haemoglobin(%)	5.46±0.23	8.6±0.22$^{\#\#\#}$	5.53±0.32***	7.49±0.42*	7.02±0.68**

Values are expressed as mean ±SEM, n=6, one way ANOVA followed by Dunnett's multiple comparisons test, ns-non significant, Compared with normal control; $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001, Compared with disease control; *p<0.05, **p<0.01, ***p<0.001.

Effect of EELA on creatinine, SGOT, SGPT and urea levels:

In diabetic rats, the effectiveness of EELA on serum SGOT, SGPT, creatinine, and urea was shown in Table 4 shows that the aforementioned

biochemical indicators significantly changed when STZ-induced diabetic rats were compared to healthy Control rats. In comparison to diabetic control rats, EELA and Glibenclamide doses significantly decreased the levels of SGOT, SGPT, creatinine, and urea in diabetic rats.

The EELA 800 mg/kg medication significantly decreased SGOT and SGPT levels when compared to the EELA 400 mg/kg dosage.

Table 4: Effect of EELA on Liver and kidney functional parameters

Parameters	**Control**	**(STZ+NIC)**	**(STZ+NIC)+ STD(20mg/kg)**	**(STZ+NIC)+ EELA(400mg/kg)**	**(STZ+NIC)+ EELA(800mg/kg)**
SGOT (U/L)	40.18±1.01	$68.27\pm2.05^{\#\#\#}$	$43.16\pm2.05^{***}$	$60.79\pm2.06^{**}$	$56.89\pm2.85^{***}$
SGPT (U/L)	48.96±0.52	$72.21\pm1.05^{\#\#\#}$	$59.89\pm5.001^{***}$	$65.64\pm1.91^{*}$	$62.97\pm0.63^{**}$
Blood Urea(mg/dl)	39.37±0.59	$59.33\pm3.54^{\#\#\#}$	$46.43\pm3.13^{***}$	$49.75\pm1.10^{**}$	$46.64\pm1.08^{***}$
Creatinine (mg/dl)	0.46±0.108	$0.088\pm0.02^{\#\#\#}$	$0.54\pm0.099^{***}$	$0.35\pm0.037^{**}$	$0.40\pm0.008^{***}$

Values are expressed as mean ±SEM, n=6, one way ANOVA followed by Dunnett's multiple comparisons test, ns-non significant, Compared with normal control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$, Compared with disease control; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

Effect of EELA on lipid profiles in STZ-induced diabetic rats:

Treatment groups exhibited considerably higher TC and TG levels than normal control rats did. When diabetic rats were administered EELA 400 and 800 mg/kg dosages, elevated TC and TG levels were dramatically lowered in comparison to diabetic control rats (Table 5).

Table 5: Effect of EELA on Total Cholesterol and Triglycerides

Parameters	**Control**	**(STZ+NIC)**	**(STZ+NIC) + STD(20mg/kg)**	**(STZ+NIC)+ EELA(400mg/kg)**	**(STZ+NIC)+ EELA(800mg/kg)**
Total Cholesterol (mg/dl)	175.6±0.8	$251.9\pm3.85^{\#\#\#}$	$179.0\pm3.21^{***}$	$232.49\pm8.059^{**}$	$220.63-\pm7.62^{***}$
Triglycerides (TG) (mg/dl)	165.56±3.22	$262.54\pm3.24^{\#\#\#}$	$166.60\pm1.05^{***}$	$250.02\pm4.91^{*}$	$216.01\pm2.144^{***}$

Values are expressed as mean ±SEM, n=6, one way ANOVA followed by Dunnett's multiple comparisons test, ns-non significant, Compared with normal control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$, Compared with disease control; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

Antioxidant activity of EELA:

The antioxidant activity of EELA in the liver was examined in diabetic rats, and the findings are shown in Table 6. STZ development of diabetes led to considerably lower levels of SOD, CAT, GPx, and decreased GSH in the liver as compared to normal control rats. These low antioxidant levels were considerably recovered in diabetic control rats after administration of EELA 400 and 800 mg/kg and glibenclamide 20 mg/kg dosages.

Table 6: Effect of EELA on enzymatic antioxidant

Parameters	**Control**	**(STZ+NIC)**	**(STZ+NIC)+ STD(20mg/kg)**	**(STZ+NIC)+ EELA(400mg/kg)**	**(STZ+NIC)+ EELA(800mg/kg)**
SOD (unit/min/ Mg protein)	8.3±0.850	$3.5\pm0.650^{\#\#\#}$	$8.3\pm0.757^{***}$	$5.9\pm0.450^{**}$	$8.3\pm0.2^{***}$
LPO (nmol MDA/ mg protein)	3.82±0.606	$34.04\pm0.603^{\#\#\#}$	$15.87\pm1.55^{***}$	$19.75\pm0.438^{***}$	16.7±0.427***
CAT (mmol of H2O2 consumed min/mg/protein)	93.53±1.593	$37.17\pm2^{\#\#\#}$	$72.84\pm2.345^{***}$	$70.56\pm0.592^{***}$	$66.56\pm2.18^{***}$
GSH (µg/mg Protein/mg of tissue extract)	9.81±0.15	$7.06\pm0.73^{\#\#\#}$	$9.45\pm0.06^{***}$	$9.19\pm0.005^{**}$	9.4±0.015***
GPX (µmoles of glutathione oxidized/min/mg protein)	0.779±0.01	$1.374\pm0.059^{\#\#\#}$	$0.661\pm0.031^{***}$	$0.989\pm0.009^{**}$	$0.748\pm0.024^{***}$

Values are expressed as mean ±SEM, n=6, one way ANOVA followed by Dunnett's multiple comparisons test, ns-non significant, Compared with normal control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$, Compared with disease control; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

Effect of EELA on Total protein, Liver glycogen and Carbohydrate metabolizing enzymes:

Due to EELA's capacity to absorb glucose, Hexokinase (glycolysis) and G6P (glycogenolysis) enzyme levels were significantly normalised after treatment with EELA 800 mg/kg and EELA 400 mg/kg. Total protein and hepatic glycogen levels increased significantly after EELA and glibenclamide administration in comparison to disease control rats. (Table 7)

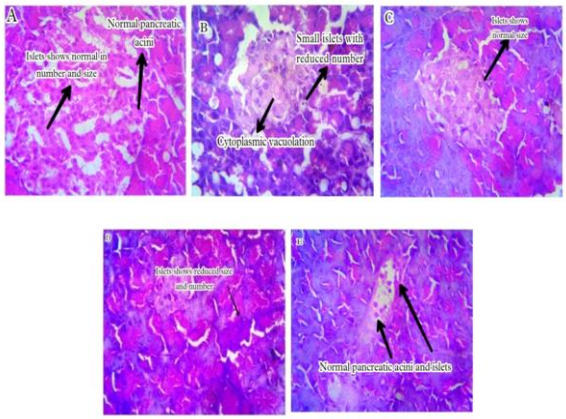
Table 7: Effect of EELA on Carbohydrate metabolizing enzymes

Parameters	Control	(STZ+NIC)	(STZ+NIC) + STD(20mg/kg)	(STZ+NIC)+ EELA(400mg/kg)	(STZ+NIC)+ EELA(800mg/kg)
Hexokinase (unit/min/mg protein)	0.4915±0.0089	$0.2609\pm0.004^{\#\#\#}$	$0.4518\pm0.0217^{***}$	$0.3256\pm0.0117^{**}$	$0.4254\pm0.0225^{***}$
Glucose-6-phosphatase (unit/min/mg protein)	0.466±0.004	$0.686\pm0.02^{\#\#\#}$	$0.600\pm0.005^{***}$	$0.588\pm0.009^{**}$	$0.538\pm0.009^{***}$
Total Protein(mg/dL)	9.1±0.771	10.3 ± 0.513^{ns}	$8.1\pm0.404^{***}$	7.2 ± 0.305^{ns}	$6.6\pm0.378^{***}$
Liver Glycogen(gm/dl)	68.6±1.026	$27.2\pm1.193^{\#\#\#}$	$54.5\pm1.123^{***}$	$44.5\pm1.30^{***}$	$51.7\pm0.493^{***}$

Values are expressed as mean ±SEM, n=6, one way ANOVA followed by Dunnett's multiple comparisons test, ns-non significant, Compared with normal control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$, Compared with disease control; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

Histopathological studies of pancreas

Histopathological alterations in the pancreas of the animals were observed using the haematoxylin–eosin (H&E) staining technique and the group IV and V animals showed regeneration of pancreatic beta cells like that of standard treated group. The results were depicted in the figure no.3



Group I: Control treated rat pancreas shows normal acini. Control treated rat islets shows normal in number and morphology. (A); Group II: STZ+NIC treated rat pancreas shows altered architecture with acini shows focal Cytoplasmic vacuolation. (B); Group III: (STZ+NIC) +Standard treated rat pancreas shows pancreatic acini. Islets shows normal in number and size with few islets shows small in size (C); Group IV: (STZ+NIC) + EELA (400mg/kg) treated rat pancreas shows normal pancreatic acini. Islets shows reduced in number and size (D); Group V: (STZ+NIC) + EELA (800mg/kg) treated rat pancreas shows normal pancreatic acini. Islets show normal in number and size (E).

Figure 3: Histopathological studies of pancreas

Discussion

In this study, the effects of an ethanolic extract of Luffa acutangula aerial parts on type II diabetic rats produced by streptozotocin-nicotinamide were examined. Body weight loss in Type-II diabetic rats compared to control rats supports the theory that diabetes was brought on by low insulin levels. Insulin controls protein synthesis and proteolysis in skeletal muscle physiologically. The pancreas' increased synthesis of insulin, the gut's decreased absorption of sugar, the liver's decreased release of glucose, and the increased uptake of glucose by fat and muscle cells are likely mechanisms at play. Consequently, EELA's prevention of STZ-NIC-mediated -cell damage in diabetic rats may account for the aforementioned benefit. Moreover, this produces an increase in insulin release and inhibits muscle proteolysis, which improves body weight in EELA-treated diabetic rats.

A steady or protracted rise in blood glucose leads to the non-enzymatic attachment of glucose to the free amino groups at the N-terminal of the beta chain of haemoglobin, resulting in glycosylated haemoglobin. Lowering HbA1c levels after diabetes treatment dramatically reduced microvascular effects, according to published study [20].

Hb levels in (STZ+NIC)-induced diabetic rats are markedly reduced, but HbA1C levels are elevated. Treatment with EELA (800 mg/kg) and EELA (400 mg/kg) reduced HbA1c and improved Hb levels on par with the control group, which may be attributable to EELA's ability to lower blood sugar by reversing insulin resistance or to boost insulin secretion by regenerating pancreatic beta cells.

The biological mechanism of type 2 diabetes has been shown to be subject to tissue damage caused by lipid peroxide. In comparison to the disease control group, the levels of CAT, SOD, and GSH rose after therapy in diabetic rats with an enhanced free radical situation, whereas the levels of LPO decreased [20].

Total protein and hepatic glycogen levels rose in diabetic control rats when EELA 800 mg/kg or EELA 400 mg/kg were administered. Hexokinase (glycolysis) and G6P (glycogenolysis) enzymes were not secreted in the liver sufficiently during diabetes, but after treatment with EELA 800 mg/kg and EELA 400 mg/kg when glucose uptake capacity was enhanced, these enzyme levels were normalised.

The hypolipidemic effect of EELA reduces triglycerides and total cholesterol. Due to liver and renal damage, diabetic rats had higher levels of SGPT, SGOT, blood urea, and creatinine. Nevertheless, after receiving EELA treatment, these levels were reduced in comparison to diabetic rats. After receiving EELA 800 mg/kg and EELA 400 mg/kg, diabetic control rats had greater levels of total protein and hepatic glycogen.

Conclusion

According to the results of the current investigation, EELA may be effective in treating Diabetes mellitus without producing any overt harmful effects. The anti-diabetic effects of EELA were comparable to those of the common medication Glibenclamide. In diabetic rats treated with EELA, blood sugar, SGPT, SGOT, blood urea, creatinine, haemoglobin, total cholesterol, triglyceride, LPO, and GPX levels were significantly lowered. Yet, in diabetic rats treated with EELA, body weight, HbA1c, CAT, SOD, GSH, hexokinase, liver glycogen, and G6P were all markedly increased. Histopathological studies have demonstrated that treatment groups experienced pancreatic beta cell regeneration. The existence of phenol, phytol, maleic anhydride, neophytadiene, furan, lutein, and eugenol in EELA has been confirmed by GC-MS analysis. The laboratory results from this investigation support the conventional usage of EELA to treat diabetes, indicating a need to isolate and assess active ingredients responsible for the demonstrated biological activity for the upcoming studies.

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