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Assessment of Antidiabetic Potential Using Melia azedarach fruit Extract

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ABSTRACT
Melia azedarach L, also known as Chinaberry tree, is a well-studied plant native to Southeast Asia. Its leaves, bark, and fruits have been traditionally used for their antiinflammatory, antipyretic, analgesic, and insecticidal properties. The plant contains bioactive compounds like flavonoids, alkaloids, terpenoids, and saponins. Recent studies have shown that extracts from Melia azedarach L have anticancer properties and antimicrobial activity against various pathogens. Ayurveda, a traditional Indian medicinal system, has been practiced for thousands of years. Research on pharmacognosy, chemistry, and clinical therapeutics has been conducted on ayurvedic medicinal plants. Modern medicine, or allopathy, has evolved over time, but its foundation remains rooted in traditional medicine and therapies. Melia azedarach Linn, also known as mahanimba, is a large evergreen tree found throughout India, used for its anthelmintic, antilithic diuretic, emmenagogue, astringent, and stomachic properties. The pharmacognostic evaluation of Melia azedarach includes the identification and characterization of its chemical constituents, which are essential for formulating an effective antidiabetic product. Assessing the antidiabetic potential of Melia azedarach fruit extract involves conducting preclinical and clinical studies to determine its efficacy and safety profile. These studies play a crucial role in establishing the plant's credibility as a natural remedy for managing diabetes. The study aims to assess the acute toxicity and anti-diabetic potential of Melia azedarach fruit extracts. Melia azedarach fruit's methanol extract (MEMA) has been found to have stronger antidiabetic action than its aqueous extract (AEMA). This is likely due to its stimulatory impact on insulin production, improving insulin-dependent gene expression, lipid profile, oxidative stress, and antioxidant defense systems. MEMA also has potent antioxidant capacity due to its high flavonoid content, which reduces damaging radicals. The presence of polyphenols contributes to its effects, including reduced oxidative stress indicators and increased antioxidant protective capacity. The hypotriglyceremic and normolipemic effects of MEMA may be due to glycosides. Thus, Melia azedarach fruit extract could be a potential diabetes treatment agent.

Keywords: *Methanolic extract of Melia azedarach, Aqueous extract of Melia azedarach, Anti Diabetic Activity, Inflammatory cytokines, Oxidative stress parameters.*

1. INTRODUCTION

Melia azedarach L, also known as Chinaberry tree, is a well-studied plant native to Southeast Asia. Its leaves, bark, and fruits have been traditionally used for their antiinflammatory, antipyretic, analgesic, and insecticidal properties (1). The plant contains bioactive compounds like flavonoids, alkaloids, terpenoids, and saponins. Recent studies have shown that extracts from *Melia azedarach* L have anticancer properties and antimicrobial activity against various pathogens. Ayurveda, a traditional Indian medicinal system, has been practiced for thousands of years. Research on pharmacognosy, chemistry, and clinical therapeutics has been conducted on ayurvedic medicinal plants (2). Modern medicine, or allopathy, has evolved over time, but its foundation remains rooted in traditional medicine and therapies. *Melia azedarach* Linn, also known as mahanimba, is a large evergreen tree found throughout India, used for its anthelmintic, antilithic diuretic, emmenagogue, astringent, and stomachic properties (3). The pharmacognostic evaluation of *Melia azedarach* includes the identification and characterization of its chemical constituents, which are essential for formulating an effective antidiabetic product. Assessing the antidiabetic potential of *Melia azedarach* fruit extract involves conducting preclinical and clinical studies to determine its efficacy and safety profile. These studies play a crucial role in establishing the plant's credibility as a natural remedy for managing diabetes. The study aims to assess the acute toxicity and anti-diabetic potential of Melia azedarach fruit extracts.

2. MATERIALS AND METHODS

2.1 Acute Toxicity Study

Total 6 rats of 10-12 weeks age were selected and randomly divided into 2 groups. Group I was vehicle control group which received vehicle (gum acacia 1% w/v in distilled water) while group II was test group that received aqueous and methanolic extracts of Melia azedarach fruit (AEMA and MEMA). Each group consisted of 3 animals (females). Females were nulliparous and non-pregnant [4].

2.2 Evaluation of aqueous and methanolic extracts of Melia azedarach fruit (AEMA and MEMA) for its Anti Diabetic potential

Fifty Sixty adult male rats weighing 180–200 g were used in the current study. Animals were randomly allocated into 7 groups (8 rats each). Group I was treated as Non diabetic Control (NPD + Saline), Group II was treated as diabetic control rats (HFD + STZ) + vehicle (gum acacia 4%) (2 ml/kg, orally), Group III was treated as Diabetic rats with Standard drug, Pioglitazone (10 mg/kg/day, orally), Group IV-V were treated as Diabetic rats treated with AEMA (150 and 300 mg/kg, orally) and Group VI-VII were treated as Diabetic rats treated with AEMA (150 and 300 mg/kg, orally). Total duration of the study will be of 60 days. Type II diabetes (NIDDM) will be induced according earlier reported method (140) with modification. Briefly, animals will be fed high fat diet (HFD), once a day for 2 weeks. After 2 weeks, animals will be fasted overnight and injected Streptozotocin (50 mg/kg, intraperitoneally) dissolved in citrate buffer (0.1 M, pH 4.5). Non diabetic control animals will be fed normal pelleted diet (NPD). Hyperglycemia will be confirmed by the elevated glucose levels in plasma, determined on day 7 after streptozotocin (STZ) injection. Only rats found with permanent NIDDM will be used for the antidiabetic study [5-7].

2.3 Evaluating Parameters

The study focuses on assessing physiological parameters in rats, including body weights, blood biochemical parameters, and lipid profiles. Blood samples are collected from fasted rats and analyzed for fasting glucose levels, glycosylated haemoglobin levels, and total cholesterol. Plasma glucose levels are estimated using the glucose oxidase-peroxidase (GOD-POD) enzymatic method, which forms hydrogen peroxide when glucose is oxidized. Plasma insulin levels are assessed using a radio immunoassay technique, which involves competition between unlabeled insulin and a specific antibody. The concentration of unknown insulin is determined through radioactivity measurement of bound fractions of samples. Oxidative stress parameters in homogenate are estimated using a radio immunoassay technique. The study aims to provide valuable insights into the health and lipid profile of rats and their potential treatment options. The study involved preparing a suspension of pancreatic tissue from a sample of pancreatic cancer cells. The tissue was washed, homogenized, and centrifuged to prepare a 10% w/v suspension. The supernatant was used to assess lipid peroxidation (LPO), catalase (CAT), superoxide dismutase (SOD) activity, and reduced glutathione (GSH) content. LPO was assessed using a method that involved adding sodium dodecyl sulfate, acetic acid, and thiobarbituric acid to the tissue homogenate. SOD activity was measured using a spectrophotometer, and catalase activity was measured using a spectrophotometer. Reduced glutathione content was measured using precipitating buffer and a test tube containing phosphate buffer and DTNB reagent. The concentrations of TNF-a, IL-6, and IL-10 in brain supernatants were estimated using commercial ELISA kits. Pancreatic tissues were preserved in 10% buffered formalin and processed using a tissue processor. The tissues were then embedded in paraffin and sections were cut into sections. The pancreatic sections were examined for morphological alterations, including the loss of pancreatic islets, hypertrophy of the pancreatic islets, and a change in the lipid composition of the exocrine pancreas. A scoring system was used to evaluate the loss of pancreatic islets and the appearance of hypertrophy pancreatic islets. The whole region of the pancreas was studied to count the number of pancreatic islets [8-10].

3. RESULTS AND DISCUSSION

3.1 Acute Toxicity Study

It was noted that the LD50 of the test substance (AEMA and MEMA are abbreviations that stand for aqueous and methanol extracts of Melia azedarach (L.) fruits, respectively) was greater than 2000 mg/kg of body weight. Based on the observation that was made during the toxicity studies, it is possible to draw the conclusion that AEMA and MEMA were safe up to a dose of 2000 mg/kg body weight. This conclusion is based on the fact that an oral dose of 2000 mg/kg body weight did not cause drug-related toxicity and mortality, abnormal clinical signs, remarkable body weight, or gross pathological changes in the animals. The test chemical is categorised as "unclassified" or "category - 5" in accordance with the Globally Harmonised approach. This is due to the fact that its LD50 was shown to be greater than 2000 mg/kg body weight.

3.2 Assessment of Anti Diabetic Action

8.6.3.1 Effect on Relative Body Weight

One-way ANOVA showed that AEMA and MEMA have significant influence on Relative Body Weight. Post hoc test indicated the Relative Body Weight was significantly increased by treatment with high dose level of AEMA and MEMA

(300 mg/kg, P<0.01) whereas the lower doses (150 mg/kg) of AEMA and MEMA did not show significant increase in the Relative Body Weight compared to NC. The standard drug, Pioglitazone (10 mg/kg/day) also showed significant (P<0.001) increase in Relative Body Weight to NC group (Figure 1).

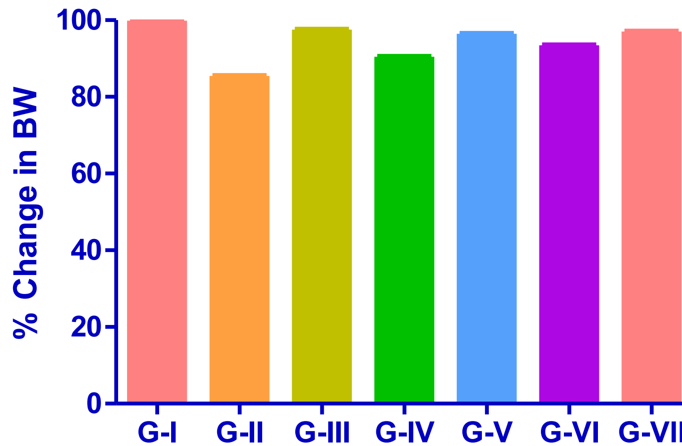

Figure 1: Effect on Relative Body Weight (BW) (G-I is Non diabetic Control, G-II is diabetic control rats, G-III is Standard treated group, G- IV and G-V are Diabetic rats treated with AEMA (150 and 300 mg/kg, orally) and G-VI and G-VII are treated as Diabetic rats treated with AEMA (150 and 300 mg/kg, orally) repectively)

8.6.3.2 Effect on Plasma Glucose Levels

One-way ANOVA showed that AEMA and MEMA have significant influence on Plasma glucose levels. Post hoc test indicated the Plasma glucose levels was significantly decreased by treatment with high dose level of AEMA and MEMA (300 mg/kg, P<0.01) whereas the lower doses (150 mg/kg) of AEMA and MEMA did not show significant decrease in the Plasma glucose levels compared to NC. The standard drug, Pioglitazone (10 mg/kg/day) also showed significant (P<0.001) decrease in Plasma glucose levels to NC group. The information displayed in representative Table 1 and Figure 2 shows the fasting Plasma glucose levels of 7 exploratory group rats amid the test time frame.

Table 1: Effect on Plasma Glucose Levels

Group	Initial day	15th day	30th day	45th day	60th day
I	82.23±1.21[a]	83.93±0.52[a]	85.82±0.61[a]	84.14±0.78[a]	85.80±1.28[a]
II	325.47±4.16[b]	331.7±28.43[b]	343.41±1.05[c]	356.04±2.73[c]	368.84±3.72[b]
III	339.64±4.60[b]	280.11±9.15[c]	181.57±4.90[b]	120.52±3.16[b]	90.30±1.34[a]
IV	341.24±0.60[b]	290.04±2.14[c]	179.01±0.11	129.22±0.70[b]	100.20±2.04[a]
V	345.17±0.59[c]	256.49±1.21[c]	201.28±1.50[c]	126.14±0.22[c]	81.31±1.23[c]
VI	343.15±0.60[b]	283.44±1.60[b]	199.14±2.60[b]	132.15±1.60[b]	95.45±0.65[b]
VII	344.52±0.67[a]	333.22±1.20[a]	198.23±0.68[a]	135.60±1.04[a]	83.33±1.54[a]

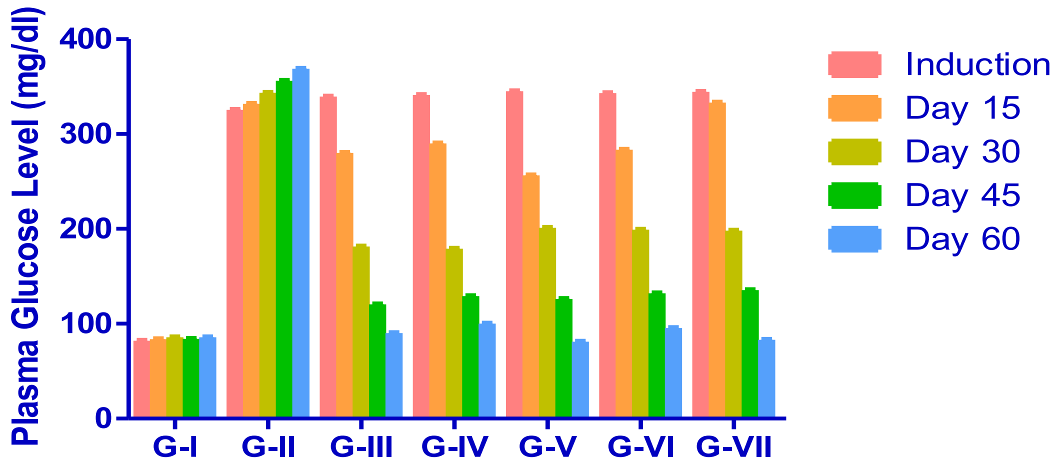

Figure 2: Effect on Plasma Glucose Levels

8.6.3.3 Effect on Plasma Insulin Levels

One-way ANOVA showed that AEMA and MEMA have significant influence on Plasma Insulin levels. Post hoc test indicated the Plasma Insulin levels was significantly increased by treatment with high dose level of AEMA and MEMA (300 mg/kg, P<0.01) whereas the lower doses (150 mg/kg) of AEMA and MEMA did not show significant increase in the Plasma Insulin levels compared to NC. The standard drug, Pioglitazone (10 mg/kg/day) also showed significant (P<0.001) increase in Plasma Insulin levels to NC group. The information displayed in representative Table 2 and Figure 3 shows the fasting Plasma Insulin levels of 7 exploratory group rats amid the test time frame.

Table 2: Effect on Plasma Insulin Levels (µUnits/ml)

Group	Initial day	15th day	30th day	45th day	60th day
I	37.97±0.46[a]	38.21±0.34[a]	39.38±0.87[a]	40.55±1.65[a]	42.27±1.59[a]
II	14.51±1.12[b]	13.27±0.08[b]	12.52±0.72[b]	11.91±0.36[b]	11.07±0.24[b]
III	16.1±0.36[a]	27.19±0.68[a]	38.47±0.51[a]	40.22±0.47[a]	41.1±1.05[a]
IV	15.01±0.36[a]	21.22±0.24[b]	30.55±0.24[b]	38.44±0.36[a]	38.99±0.24[b]
V	14.91±0.34[b]	16.67±0.66[c]	20.97±0.56[c]	27.32±0.89[c]	34.61±0.88[c]
VI	15.99±0.24[b]	19.21±0.36[a]	29.26±0.24[b]	32.44±0.24[b]	39.45±0.36[a]
VII	13.31±0.33[C]	18.87±1.24[c]	28.18±1.25[c]	34.41±0.59[c]	43.97±0.51[c]

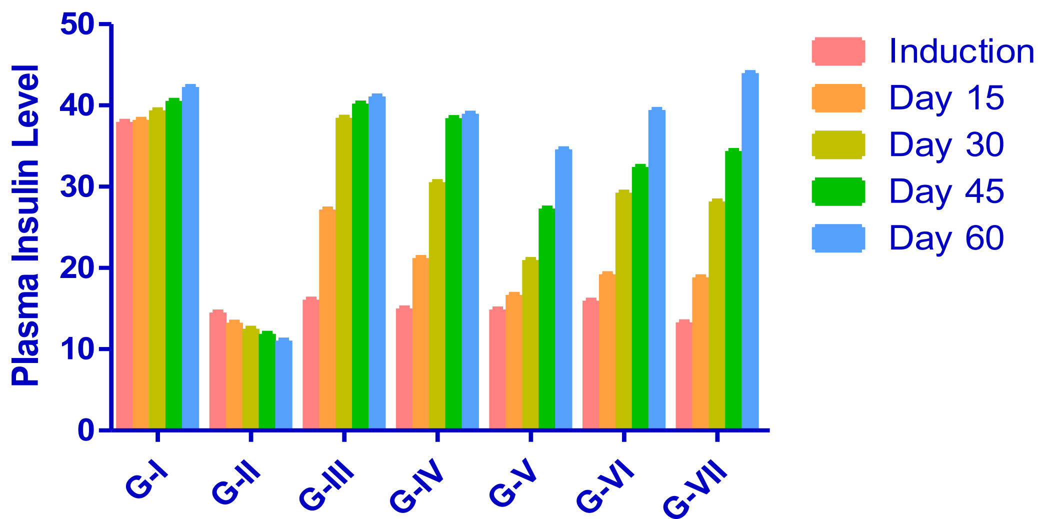

Figure 3: Effect on Plasma Insulin Levels (µUnits/ml)

8.6.3.4 Effect on Lipid Profile in Blood Plasma

One-way ANOVA showed that AEMA and MEMA have significantly influenced the Lipid Profile levels. Post hoc test indicated the Plasma Insulin levels was significantly influenced the Lipid Profile levels by treatment with high dose level of AEMA and MEMA (300 mg/kg, P<0.01) and standard drug, Pioglitazone (10 mg/kg/day) whereas the lower doses (150 mg/kg) of AEMA and MEMA did not show significant changes compared to NC. The information displayed in representative Table 3 shows the fasting influenced the Lipid Profile levels of 7 exploratory group rats amid the test time frame.

Table 3: Effect on Lipid Profile in Blood Plasma

Parameters	G-I	G-II	G-III	G-IV	G-V	G-VI	G-VII
Total lipids (mg/g tissue)	340.36 ±13.42	127.15 ±16.32^{a}	258.27 ±4.56^{b}	307.12 ±5.32^{c}	321.15 ±2.21^{d}	319.15 ±0.21^{d}	311.15 ±5.32^{c}
Phospholipids (mg/g tissue)	67.42 ±1.45^{c}	43.32 ±2.12^{a}	54.72 ±1.15^{b}	62.11 ±1.32^{c}	60. 21 ±1.11^{d}	59. 21 ±0.12^{d}	60.61 ±1.32^{c}
Triglycerides (mg/g tissue)	7.84 ±0.12^{a}	12.14 ±0.31^{d}	7.96 ±0.54^{c}	7.63 ±0.22^{b}	7.78 ±0.13^{c}	7.80 ±0.55^{c}	6.69 ±0.22^{b}
Cholesterol (mg/g tissue)	30.21 ±0.85^{d}	22.51 ±1.24^{a}	27.43 ±0.51^{c}	28.82 ±0.23^{c}	29.74 ±0.21^{a}	30.04 ±0.21^{a}	27.00 ±0.23^{c}
Glycolipids (mg/g tissue)	3.72 ±0.16^{c}	1.01 ±0.11^{a}	2.43 ±0.21^{b}	4.82 ±0.23^{d}	2.95 ±0.85^{c}	3.00 ±0.69^{c}	3.82 ±0.25^{d}

8.6.3.5 Effect on the Oxidative Stress Parameters

One-way ANOVA showed that administration of AEMA and MEMA (300 mg/kg, P<0.01) and standard drug, Pioglitazone (10 mg/kg/day) exhibited significantly (P<0.01-P<0.01) influenced the Oxidative stress parameters level in rats. The post hoc test exhibited that there is significant (P<0.001) altered the Oxidative stress parameters level in Experimental Control mice compared to Normal Control mice. Concurrent treatment with AEMA and MEMA (300 mg/kg, P<0.01) and standard drug, Pioglitazone (10 mg/kg/day) exhibited significant (P<0.01-P<0.01) decline in Oxidative stress parameters level as compared to EC group mice. The treatment also significantly (P<0.001) affects the Oxidative stress parameters level as

compared to EC rats (Figure 4-7).

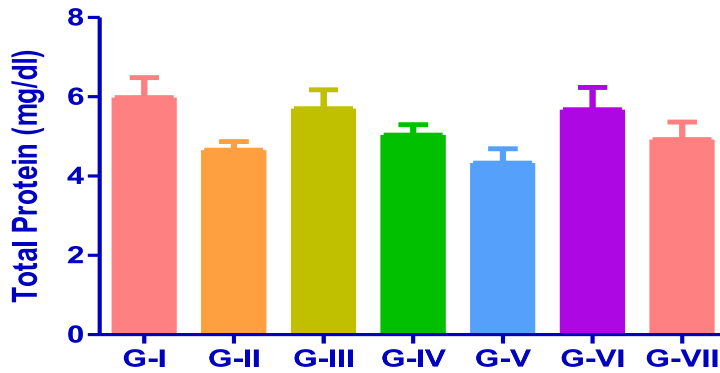

Figure 4: Estimation of Total Protein in Pancreas Homogenate

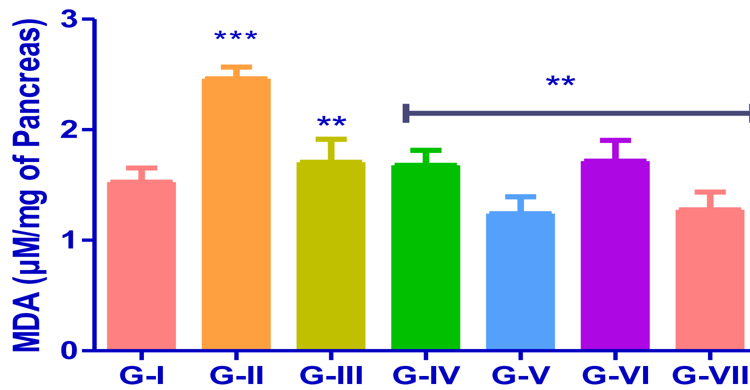

Figure 5: Estimation of LPO in Pancreas Homogenate

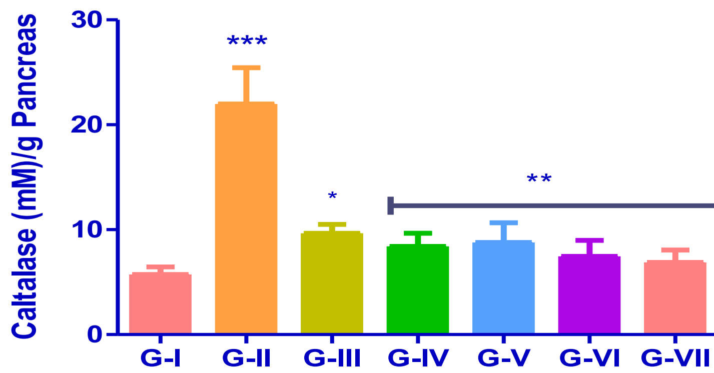

Figure 6: Estimation of Catalase in Pancreas Homogenate

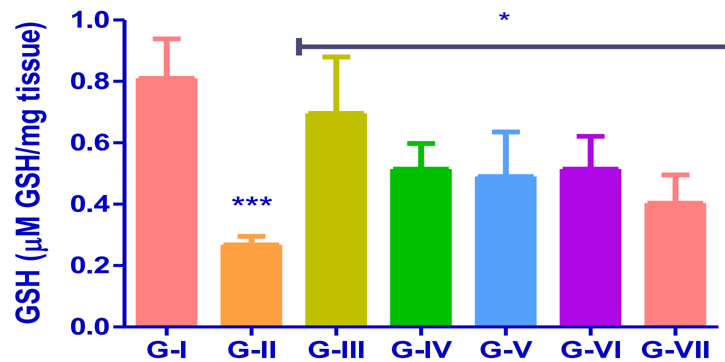

Figure 7: Estimation of Reduced Glutathione (GSH) in Pancreas Homogenate

8.6.3.6 Effect on the Cytokine Levels (TNF-α and IL-6)

One-way ANOVA showed that administration of AEMA and MEMA (300 mg/kg, P<0.01) and standard drug, Pioglitazone (10 mg/kg/day) exhibited significantly (P<0.01-P<0.01) influenced the Cytokine Levels (TNF-α and IL-6) in rats. The post hoc test exhibited that there is significant (P<0.001) altered the Cytokine Levels (TNF-α and IL-6) in Experimental Control mice compared to Normal Control rats. Concurrent treatment with AEMA and MEMA (300 mg/kg, P<0.01) and standard drug, Pioglitazone (10 mg/kg/day) exhibited significant (P<0.01-P<0.01) decline in Cytokine Levels (TNF-α and IL-6) as compared to EC group mice. The treatment also significantly (P<0.001) affects the Cytokine Levels (TNF-α and IL-6) as compared to EC rats (Figure 8 and 9).

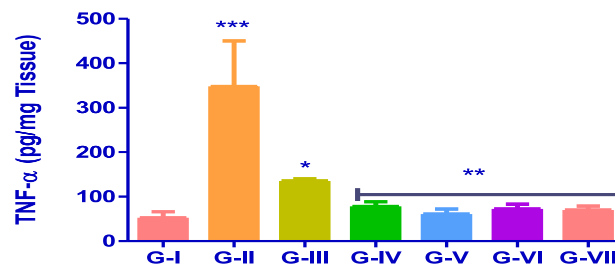

Figure 8: Effect on TNF-α level

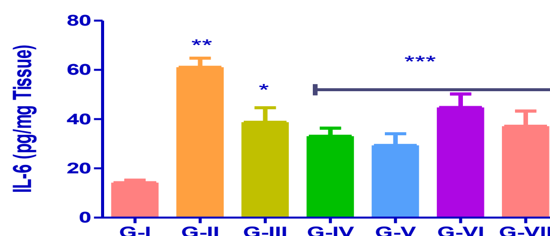

Figure 9: Effect on IL-6 level

8.6.3.7 Histopathology of Pancreas

In a diabetic rat's pancreas, histopathological examination typically reveals a significant reduction in the number and size of pancreatic islets (islets of Langerhans), particularly the beta cells responsible for insulin production, leading to a loss of normal islet architecture, sometimes accompanied by cellular degeneration, infiltration of inflammatory cells, and potential

damage to the surrounding exocrine acinar cells; essentially, the pancreas shows signs of significant beta cell destruction and impaired insulin secretion. Histomorphological features in H & E-stained pancreatic tissues of rats are presented in Figure 10. The pancreatic islets of healthy rats were normal in size with well demarcated borders. HFD feeding resulted in pancreatic islet hypertrophy. Subsequent STZ injection caused mild to severe loss of pancreatic islets (Table 4). However, the increase in number of pancreatic islets with hypertrophy was also evident in STZ-induced rats. The hypertrophic pancreatic islets of STZ-induced rats had irregular borders in contrast to HFD group rats where the hypertrophic pancreatic islets were elongated in shape with regular borders. STZ injection also resulted in a mild fatty change in the exocrine pancreas.

Table 4: Histomorphological Changes of the Pancreas

Groups	Loss of pancreatic islets	Hypertrophic pancreatic islets	Fatty change in the exocrine pancreas
I	0.0±0.000	0.0±0.000	0.0±0.000
II	3.10±0.215	2.99±0.452	3.04±0.410
III	0.78±0.011	1.54±0.552	1.69±0.005
IV	2.22±0.154	2.88±1.105	2.14±0.058
V	1.9±0.690	0.9±0.069	1.0±0.041
VI	1.99±0.044	2.01±0.085	1.99±0.055
VII	0.9±0.040	0.9±0.0044	1.11±0.152

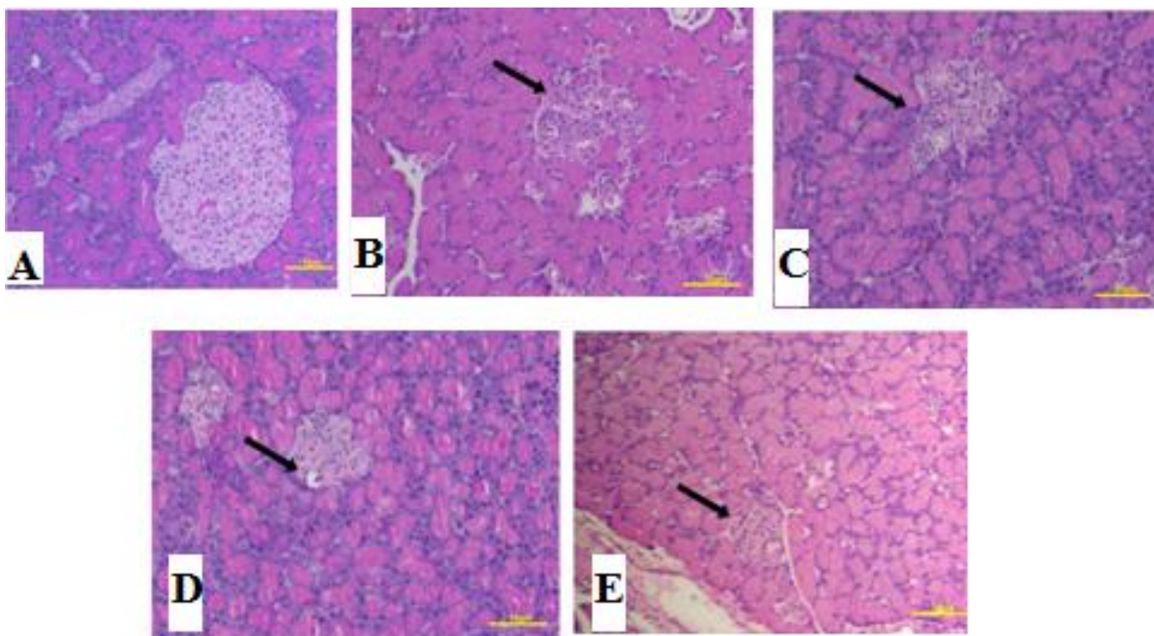

Figure 10: Histomorphological Changes of the Pancreas (A: Normal Control; B: Diabetic Control; C: Standard Treated Group; D: AEMA High dose Treated Group and E: MEMA High dose Treated Group

4. CONCLUSIONS

Melia azedarach fruit's methanol extract (MEMA) has been found to have stronger antidiabetic action than its aqueous extract (AEMA). This is likely due to its stimulatory impact on insulin production, improving insulin-dependent gene expression, lipid profile, oxidative stress, and antioxidant defense systems. MEMA also has potent antioxidant capacity due to its high flavonoid content, which reduces damaging radicals. The presence of polyphenols contributes to its effects, including reduced

oxidative stress indicators and increased antioxidant protective capacity. The hypotriglyceremic and normolipemic effects of MEMA may be due to glycosides. Thus, Melia azedarach fruit extract could be a potential diabetes treatment agent.

5. CONFLICT OF INTEREST

None

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