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Anti‐Inflammatory and Hepatoprotective Roles of Oleic and Linoleic Acids in a Wistar Rat Model of Type 2 Diabetes

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Running title

Fatty Acids and Hepatic Protection in Diabetes

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Abstract

Background: The global rise in type 2 diabetes mellitus (T2DM) poses a major healthcare challenge, driven by chronic inflammation, oxidative stress, and hepatic dysfunction. Conventional therapies primarily target glycemic control but often fail to address tissue-level injury. Dietary fatty acids such as oleic acid (OA) and linoleic acid (LA) may offer adjunctive therapeutic benefits. **Methods:** Eighty male Wistar rats (150–180g) were induced with T2DM using 10% fructose supplementation for six weeks followed by a single intraperitoneal injection of streptozotocin (35 mg/kg). Animals with fasting blood glucose >250 mg/dL were randomized into eight groups (n = 10): normal control, non-diabetic + OA, non-diabetic + LA, diabetic control, diabetic + OA, diabetic + LA, diabetic + OA+LA, and diabetic + metformin. Treatments lasted six weeks. Plasma and pancreatic cytokines, oxidative stress markers, hepatic injury enzymes, and histological changes in liver and pancreas were assessed. **Results:** Compared with diabetic controls, OA and LA significantly reduced pro-inflammatory cytokines (TNF-α, IL-6), increased anti-inflammatory IL-10, lowered malondialdehyde levels, and enhanced antioxidant enzyme activities (CAT, SOD) ($p < 0.0001$). Hepatic injury markers were normalized, and histological analysis revealed improved hepatic and pancreatic architecture. Combined OA+LA treatment produced synergistic benefits, including enhanced PDX-1 expression and greater histological restoration, though effects varied across parameters. Overall, OA and LA demonstrated efficacy comparable to metformin. **Conclusion:** Oleic and linoleic acids exert anti-inflammatory, antioxidant, and hepatoprotective effects in a rat model of T2DM. Their combined administration showed synergistic benefits, underscoring the translational potential of dietary fatty acid modulation as an adjunctive strategy for managing T2DM-associated complications.

Keywords: Oleic acid, Linoleic acid, anti-inflammatory, antioxidant, hepatoprotective, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder marked by low-grade inflammation, insulin resistance, and progressive hepatic dysfunction. These changes promote steatosis and increase the risk of non-alcoholic fatty liver disease (NAFLD) and steatohepatitis. Persistent inflammatory signaling—driven by cytokine dysregulation, lipid accumulation, and oxidative stress creating a vicious cycle that amplifies hepatocellular injury and impairs systemic glucose homeostasis (Erhunmwunse et al., 2025).

Dietary fatty acids play a central role in modulating these pathways. As structural components of membranes and precursors for bioactive molecules, their biological effects depend on chain length and degree of unsaturation (Ali et al., 2023). Unsaturated fatty acids, including monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs), influence receptor activity, intracellular signaling, and lipid raft composition, thereby shaping inflammatory tone and metabolic outcomes (Ravaut et al., 2020; Calder et al., 2024). Compared to saturated fats, MUFAs and PUFAs generally reduce lipotoxic stress, enhance insulin signaling, and mitigate oxidative damage, although their effects vary with dose and dietary balance (Tutunchi et al., 2020).

Oleic acid (18:1 n-9), the predominant MUFA in many diets, supports membrane fluidity, promotes lipid droplet formation, activates PPARα/γ pathways, and suppresses pro-inflammatory cascades such as TLR4–NF-κB (Niero et al., 2023). These actions preserve hepatocyte function

and insulin responsiveness under metabolic stress. Linoleic acid (18:2 n-6), the most abundant dietary PUFA, contributes to membrane structure and serves as a substrate for oxylipins and eicosanoids (Djuricic et al., 2021). Depending on enzymatic pathways, linoleic acid metabolites can exert either pro- or anti-inflammatory effects, with balanced metabolism favoring hepatoprotection and dysregulated conversion promoting inflammation (Du et al., 2024).

This study explores the combined anti-inflammatory and hepatoprotective effects of oleic and linoleic fatty acids in a Wistar rat model of T2DM. By harnessing their complementary bioactivities, the intervention reflects dietary patterns associated with improved metabolic health. The synergistic administration of oleic and linoleic acids produced greater therapeutic benefits than either fatty acid alone, highlighting this combination as a promising nutritional strategy for integrated diabetes management.

Materials and Methods

Instruments and Reagents

The study employed an analytical balance, metabolic cages, centrifuge, spectrophotometer, and a OneTouch glucometer with test strips. ELISA kits (Foortress Diagnostics Limited, United Kingdom) were used for biochemical assays. Reagents included fructose, D-glucose, oleic acid, linoleic acid, streptozotocin, metformin (500 mg), citric acid, sodium citrate, phosphate buffer solution (PBS), NBS, and normal saline. Standard pelleted diets were obtained from ABUAD Farms.

Animal Grouping and Treatment

Eighty (80) male Wistar rats weighing 150–180 g were housed in plastic cages at the ABUAD animal facility under controlled environmental conditions (12-h light/dark cycle, 22 ± 2 °C) and

acclimatized for 14 days with free access to water and a standard pelleted diet. Diabetes was induced by administering a 10% fructose solution in drinking water for six weeks, followed by a single intraperitoneal injection of streptozotocin (STZ, 35 mg/kg), as previously described by Ivanov et al. (2023). Animals with fasting blood glucose levels >250 mg/dL were classified as diabetic. After confirmation of diabetic status, rats were randomly assigned into eight groups (n = 10 per group): Normal control (saline only); Non-diabetic + oleic acid (10 mg/kg); Non-diabetic + linoleic acid (10 mg/kg); Diabetic control (T2DM) (untreated); Diabetic + oleic acid (10 mg/kg); Diabetic + linoleic acid (10 mg/kg); Diabetic + oleic + linoleic acids (10 mg/kg each); and Diabetic + metformin (100 mg/kg).

Ethical Approval

All experimental procedures involving animals were conducted in accordance with international guidelines for the care and use of laboratory animals. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Afe Babalola University, Ado-Ekiti (Approval No. ABUADHREC/15/01/2025/732). Efforts were made to minimize animal suffering and to reduce the number of animals used.

Sample Collection and Tissue Preparation

At the end of treatment, animals were anesthetized intraperitoneally with pentobarbital sodium (50 mg/kg). Blood samples were obtained via cardiac puncture into heparinized tubes and centrifuged at 3000 rpm for 15 minutes at room temperature; plasma was aliquoted and stored for biochemical analysis. The liver and pancreas were excised, rinsed in cold saline, and preserved for evaluation. Approximately 5 g of liver tissue and 500 mg of pancreatic tissue were

homogenized in PBS, centrifuged at 3000 rpm for 15 minutes, and the supernatants collected for subsequent assays.

Biochemical Analyses

Inflammatory and Anti-inflammatory Cytokines

Plasma and pancreatic levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10) were quantified using rat ELISA kits (Foortress Diagnostics Limited, United Kingdom), following the manufacturer's instructions and protocols described by Ezike et al. (2025).

Liver Function Markers

Gamma-glutamyl transferase (GGT) and aspartate aminotransferase (AST) activities in plasma and liver tissue were measured using commercial kits (Foortress Diagnostics Limited, United Kingdom), as outlined by Engin et al. (2024).

Oxidative Stress, Antioxidant Status, and Lipid Peroxidation

Markers of oxidative stress and antioxidant defense—including malondialdehyde (MDA), catalase (CAT), and superoxide dismutase (SOD)—were assessed in plasma and pancreatic tissue using rat ELISA kits (Foortress Diagnostics Limited, United Kingdom), in line with procedures reported by Ezike et al. (2025).

Immunohistochemical Staining Procedure for PDX-1

Immunohistochemical staining for pancreatic PDX-1 protein expression was performed as previously described by Bocchini et al. (2020), using PDX-1 polyclonal antibody kits (Elabscience Bionovation Inc) according to the manufacturer's protocol. Briefly, paraffin-embedded sections were dewaxed, rehydrated, and subjected to antigen retrieval. Endogenous peroxidase activity was blocked with 3% H_2O_2, and non-specific binding was minimized using normal goat blocking buffer. Sections were incubated with primary antibodies (mouse or rabbit origin) followed by polyperoxidase-conjugated secondary antibodies. Visualization was achieved with freshly prepared DAB substrate, and positive signals appeared as brown deposits. Slides were counterstained with hematoxylin, dehydrated, cleared in xylene, and mounted for microscopic examination.

Histological Staining (Hematoxylin and Eosin, H&E)

Hematoxylin and eosin (H&E) staining was performed on paraffin-embedded liver and pancreatic tissue sections using standard histological techniques, as previously described by Ibrahim et al. (2025). Briefly, sections were deparaffinized in xylene, rehydrated through graded ethanol, and stained with hematoxylin followed by eosin. Slides were then dehydrated, cleared in xylene, and mounted with coverslips. Photomicrographs were acquired using a high-resolution digital microscope camera (Moticam X3, 12.0 MP) attached to an OPTO-Edu Industrial Light Microscope (China). Images were captured under uniform lighting and magnification using Motic Images Plus software, and quantitative analysis was performed with ImageJ.

Statistics Analysis

All experimental data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism software (version 8.4, GraphPad Software, San

Diego, CA, USA). Group differences were assessed by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for pairwise comparisons. A p-value of <0.05 was considered statistically significant

Results

Effects of Oleic and Linoleic Acid Treatment on Plasma and Pancreatic Inflammatory Markers in Type 2 Diabetic Male Wistar Rats

In the diabetic control group (T2DM), plasma and pancreatic cytokine levels showed marked elevation of TNF-α (Fig. 1A–B) and IL-6 (Fig. 1C), accompanied by a significant reduction in IL-10 (Fig. 1D–E) (****$p<0.0001$), consistent with persistent inflammation characteristic of T2DM pathogenesis. In contrast, treatment with either oleic acid (OA) or linoleic acid (LA) significantly reduced pro-inflammatory cytokines TNF-α (Fig. 1A–B) and IL-6 (Fig. 1C), while upregulating the anti-inflammatory cytokine IL-10 (Fig. 1D–E) in both plasma and pancreatic tissue (****$p<0.0001$), indicating a robust immunomodulatory effect. However, the combined OA+LA treatment did not produce additional reductions beyond those observed with individual treatments, suggesting no additive or synergistic effect on cytokine modulation

Effects of Oleic and Linoleic Acid Treatment on Oxidative Stress Markers

Plasma and pancreatic levels of the oxidative stress marker malondialdehyde (MDA) (Fig. 2A–B) were significantly elevated in the T2DM control group (****$p<0.0001$), indicating pronounced oxidative stress and tissue damage. In contrast, treatment with either oleic acid (OA)

or linoleic acid (LA) markedly reduced MDA levels (Fig. 2A–B), while simultaneously upregulating the antioxidant enzymes catalase (CAT) (Fig. 2C–D) and superoxide dismutase (SOD) (Fig. 2E–F). These changes confirm the antioxidative properties of OA and LA and their role in restoring redox balance in T2DM (****p<0.0001).

Effects of Oleic and Linoleic Acids Treatment on Plasma and Hepatic Markers

Plasma and hepatic concentrations of aspartate aminotransferase (AST) (Fig. 3A–B) and γ-glutamyl transferase (GGT) (Fig. 3C–D) were significantly elevated in the T2DM control group (AST: ***p<0.001; ****p<0.0001; GGT: ****p<0.0001), indicating impaired hepatic function and hepatocellular injury associated with diabetes. In contrast, treatment with either oleic acid (OA) or linoleic acid (LA) significantly reduced both plasma and hepatic AST (Fig. 3A–B) and GGT (Fig. 3C–D) levels **(*****p<0.001; ****p<0.0001), demonstrating a protective effect against diabetes-induced liver injury. Although the combined OA+LA treatment group showed a trend toward greater efficacy, the difference was not statistically significant, suggesting that these fatty acids exert hepatoprotective effects primarily through individual rather than additive mechanisms.

PDX-1 Expression In The Pancreatic Tissue

Pancreatic tissue from the T2DM control group (G4) exhibited a significant downregulation of pancreatic and duodenal homeobox 1 (PDX-1) expression (****p < 0.0001), indicating impaired pancreatic function. In contrast, all treatment groups showed markedly higher PDX-1 expression levels compared with the diabetic control (Fig. 4), consistent with improved pancreatic activity. Notably, the combined OA+LA treatment produced the greatest increase in PDX-1 expression,

surpassing the effects of individual fatty acids, thereby highlighting a synergistic role in promoting pancreatic regeneration.

Effects of Oleic and Linoleic Acids Treatment on Hepatic Steatosis

H&E staining revealed normal hepatic architecture in the positive control groups (G1–G3; histology score = 0). In contrast, the T2DM control group (G4) showed severe abnormalities, including microvesicular steatosis, hepatocyte degeneration, vascular congestion, and high histology scores. Treatment with oleic acid (G5), linoleic acid (G6), or their combination (G7) improved hepatic morphology, with reduced fat vacuoles, less congestion, and lower histology scores. Notably, the OA+LA group (G7) and metformin group (G8) both exhibited mild histology scores, reflecting comparable restoration of hepatic structure (Fig. 5)

Effects of Oleic and Linoleic Acids Treatment on Pancreatic Steatosis & Degeneration

The H&E staining revealed normal pancreatic architecture in the positive control groups (G1–G3), with intact endocrine cells and normal islet counts (****$p<0.0001$). In contrast, the T2DM control group (G4) showed severe abnormalities, including endocrine cell degeneration, reduced islet counts, and lipid vacuoles indicative of steatosis. Treatment with oleic acid (G5), linoleic acid (G6), or their combination (G7) improved morphology, with reduced degeneration, restored islet counts, and diminished fat vacuoles (**$p<0.01$; ***$p<0.001$). Notably, the combined OA+LA group (G7) exhibited the most pronounced protective effects (Fig. 6).

Discussion

This study demonstrates that oleic acid (OA) and linoleic acid (LA), administered alone or in combination, attenuate systemic and pancreatic inflammation, reduce oxidative stress, and

restore hepatic injury markers in a rat model of type 2 diabetes mellitus (T2DM). Compared with diabetic controls, treated groups showed reduced TNF-α and IL-6, elevated IL-10, lower MDA, enhanced SOD and CAT activities, and normalized AST and GGT. The combined OA+LA regimen produced the largest effect size in several endpoints, suggesting complementary anti-inflammatory and hepatoprotective actions (Sivri et al., 2025; Demirdağ et al., 2023). However, this effect was not consistent across all parameters, as some outcomes showed comparable improvements with individual treatments.

Because inflammation is a central driver of insulin resistance and β-cell dysfunction, these systemic changes can be mechanistically linked to the suppression of NF-κB and JNK signaling, which otherwise impair IRS activity (Shaw et al., 2025; Aranda et al., 2024). The cytokine profile in diabetic controls matched this pathogenic pattern, while OA and LA reversed these changes, indicating immune modulation rather than symptomatic suppression. The combined treatment suggests complementary fatty acid pathways converge to inhibit NF-κB transcription while promoting anti-inflammatory mediators, potentially via AMPK and PPARα/γ activation (Demirdağ et al., 2023). These findings align with prior reports that unsaturated fatty acids downregulate inflammatory cascades and improve insulin signaling (Miklankova et al., 2022; Zhu et al., 2020; Basak et al., 2020).

Inflammation and oxidative stress are tightly interconnected in T2DM, as hyperglycemia enhances ROS generation through glucose autoxidation, polyol flux, AGE formation, and mitochondrial dysfunction, overwhelming antioxidant defenses (Singh et al., 2022; Jena et al., 2023). Elevated MDA and reduced antioxidant enzymes in diabetic controls confirmed oxidative damage. OA and LA reduced MDA and restored SOD and CAT, consistent with enhanced

antioxidant capacity. Mechanistically, these effects may involve upregulation of antioxidant enzymes, mitochondrial stabilization, inhibition of pro-oxidant systems, and improved glutathione turnover (Alum et al., 2025). These results corroborate studies on oleic acid's mitochondrial and endothelial benefits (Rehman et al., 2020; Munteanu et al., 2025; Wang et al., 2023; Lattibeaudiere et al., 2024).

The liver, as a metabolic hub, integrates these inflammatory and oxidative signals. Insulin resistance drives gluconeogenesis, lipogenesis, and lipid accumulation, promoting NAFLD and hepatocellular injury (Frankowski et al., 2023; Li et al., 2025). Elevated AST and GGT in diabetic controls reflected hepatic stress. OA and LA normalized these enzymes, with the combined regimen producing near-complete restoration, comparable to metformin. This suggests direct hepatoprotective effects mediated by reduced hepatic inflammation, improved mitochondrial efficiency, and modulation of lipid metabolism. These findings are consistent with prior nutritional studies (Lattibeaudiere et al., 2024; Pertiwi et al., 2020; Ma et al., 2023).

Pancreatic histology further integrates these systemic improvements. Chronic hyperglycemia and lipotoxicity impair β-cell survival, leading to islet degeneration and steatosis (Suzuki et al., 2024). In our study, OA and LA ameliorated these abnormalities, reducing islet degeneration and fat vacuoles. Importantly, the combined OA+LA group showed more pronounced improvements than individual treatments, indicating a synergistic interaction that may enhance β-cell survival, insulin transcription, and glycemic regulation.

Taken together, OA and LA exert complementary actions—immune modulation, redox restoration, and metabolic reprogramming—via suppression of NF-κB/JNK, enhancement of IL-10, induction of antioxidant defenses, and activation of AMPK/PPAR pathways (Demirdağ et

al., 2023; Alum et al., 2025). The superior efficacy of the combined treatment suggests true synergy, where each fatty acid targets overlapping but distinct molecular nodes.

Strengths of this study include a comprehensive panel of inflammatory, oxidative, hepatic, and pancreatic endpoints, as well as direct comparison with metformin. Limitations include reliance on a single animal model, short treatment duration, absence of molecular readouts (e.g., NF-κB phosphorylation, AMPK activation), and lack of microbiota profiling (Zhu et al., 2020). Dose-response and pharmacokinetic studies are warranted, and extrapolation to humans requires caution due to dietary context and interspecies differences.

Conclusion

Oleic and linoleic acids exert complementary anti-inflammatory, antioxidant, and hepatoprotective effects in T2DM. Across multiple endpoints, both fatty acids improved cytokine balance, reduced oxidative stress, normalized hepatic enzymes, and preserved pancreatic and hepatic histoarchitecture. The combined OA+LA treatment produced more pronounced benefits in selected outcomes—such as PDX-1 expression and histological restoration—though not consistently across all parameters. Importantly, its comparable efficacy to metformin underscores the translational relevance of dietary fatty acid modulation as a potential adjunctive strategy for managing T2DM complications. Future studies should define dose-response relationships, clarify molecular mechanisms, and evaluate long-term outcomes to establish therapeutic potential in clinical settings.

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Conflict of Interest

The authors declare that they have no conflict of interest

Consent for publication

For this type of study consent for publication is not required

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Results

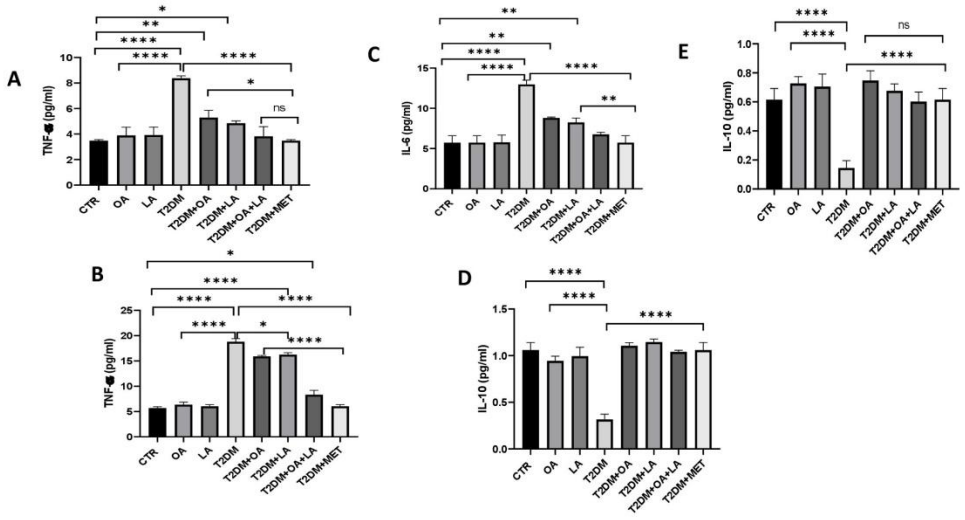


Figure 1: Effect of oleic acid (OA) and linoleic acid (LA) treatment on plasma and pancreatic inflammatory markers in type 2 diabetic male Wistar rats. Values are significant ($p < 0.05$) compared with control groups (CTR, AO, LA), diabetic control (T2DM), oleic treatment (T2DM+OA), linoleic treatment (T2DM+LA), combined OA+LA treatment (T2DM+OA+LA), and metformin treatment (T2DM+MET).

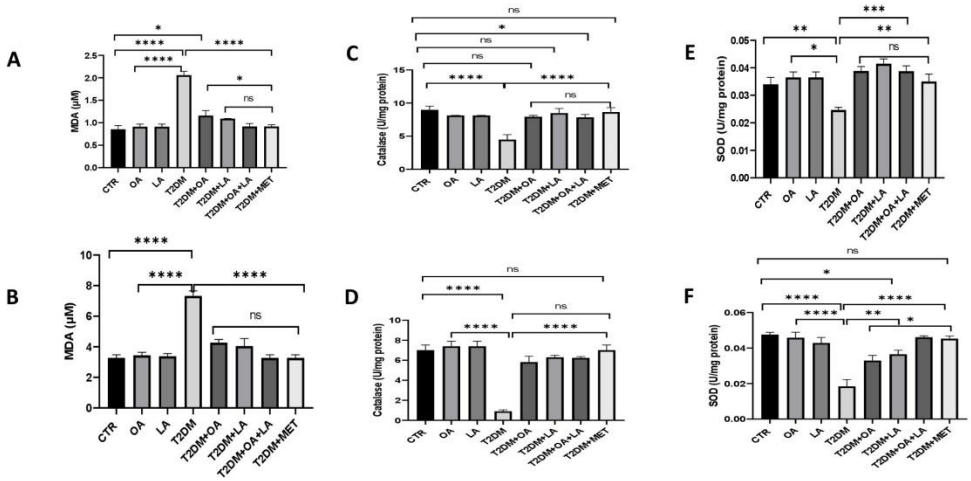


Figure 2: Effect of OA & LA treatment on the plasma and pancreatic oxidative and anti-oxidative stress Markers in Type 2 Diabetic Male Wistar ($p < 0.05$) significant compared with control (CTR, AO, LA) and diabetic control (T2DM), and Oleic (T2DM+OA) and linoleic treatment groups (T2DM+OA), oleic and linoleic combined treatment group (T2DM+OA +LA) and metformin treatment group (T2DM+MET).

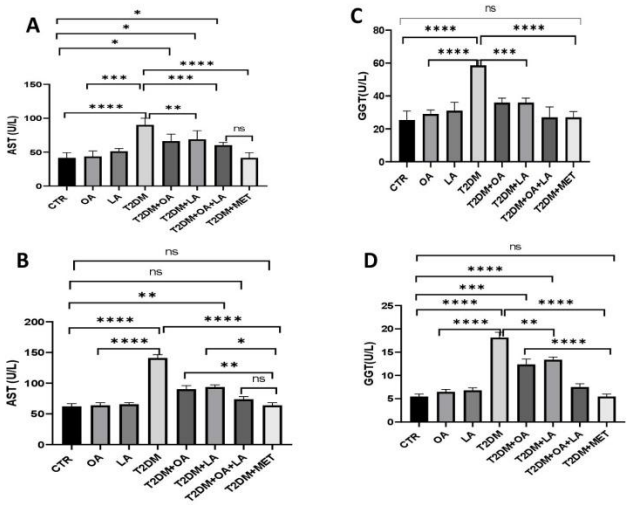


Figure 3: Effect of OA & LA treatment on the plasma and liver function Markers in Type 2 Diabetic Male Wistar Rats ($p < 0.05$) significant compared with control (CTR, AO, LA) and diabetic control (T2DM), and Oleic (T2DM+OA) and linoleic treatment groups (T2DM+OA), oleic and linoleic combined treatment group (T2DM+OA +LA) and metformin treatment group (T2DM+MET).

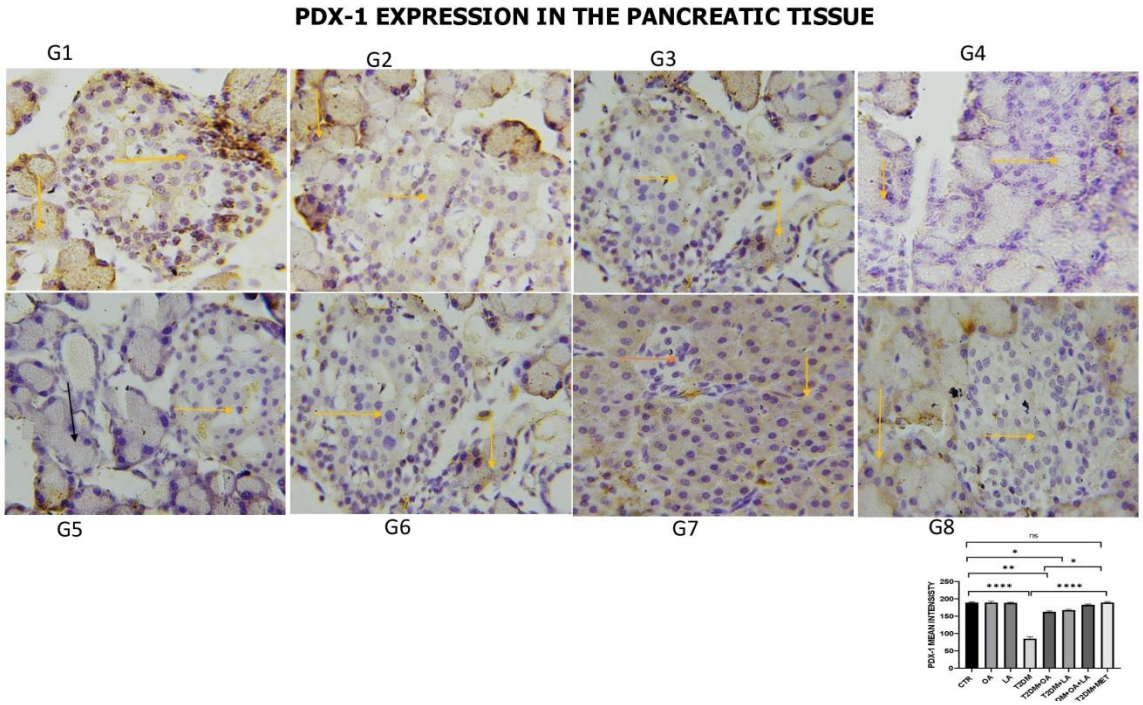
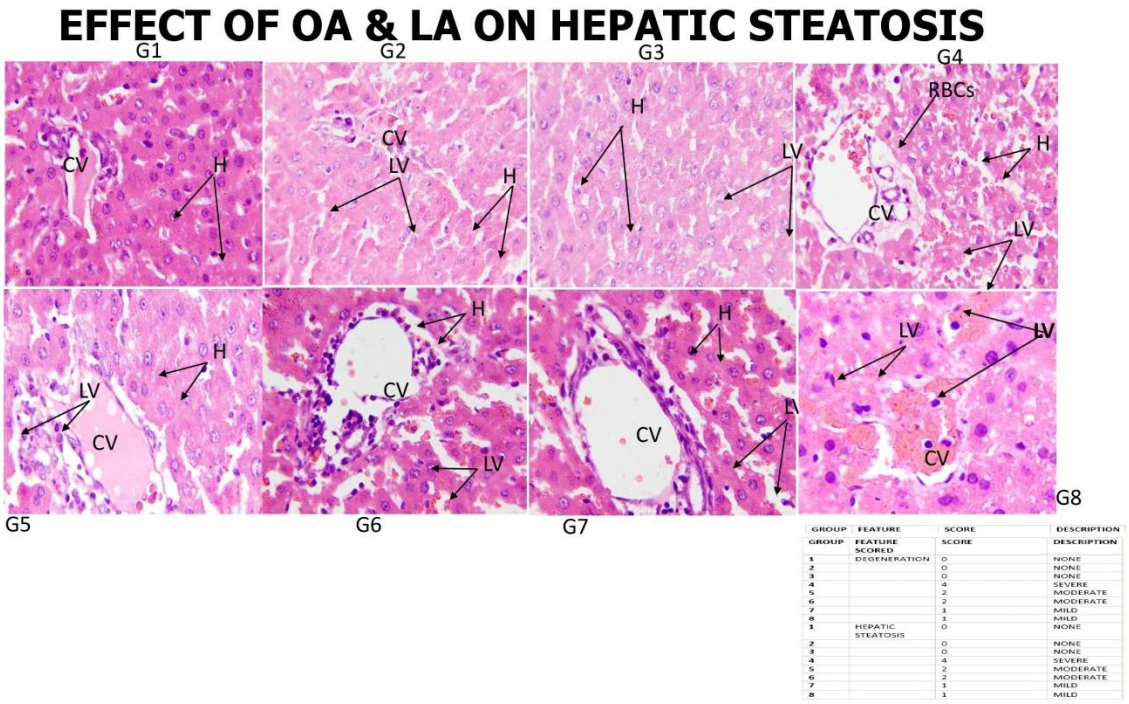


Figure 4: Photomicrograph showing IHC of PDX-1 protein expression in the pancreatic tissue among the experimental groups. G1: normal control (CTR), GP2: oleic acid only (OA), G3: linoleic acid only (LA), G4: diabetic control (T2DM), G5: oleic Group (T2DM+OA+LA) and metformin treated group (T2DM+MET) (Mag. x800).



GROUP	FEATURE SCORED	SCORE	DESCRIPTION
1	DEGENERATION	0	NONE
2		0	NONE
3		0	NONE
4		4	SEVERE
5		2	MODERATE
6		2	MODERATE
7		1	MILD
8		1	MILD
1	HEPATIC STEATOSIS	0	NONE
2		0	NONE
3		0	NONE
4		4	SEVERE
5		2	MODERATE
6		2	MODERATE
7		1	MILD
8		1	MILD

Figure 5: H&E-stained liver section showing hepatic steatosis among the experimental groups. G1: normal control (CTR), GP2: oleic acid only (OA), G3: linoleic acid only (LA), G4: diabetic control (T2DM), G5: oleic Group (T2DM+OA), G6: linoleic acid treatment group (T2DM+LA), G7: oleic & linoleic acid combined treatment group (T2DM+OA+LA) and G8: metformin treated group (T2DM+MET) (Mag. x800).

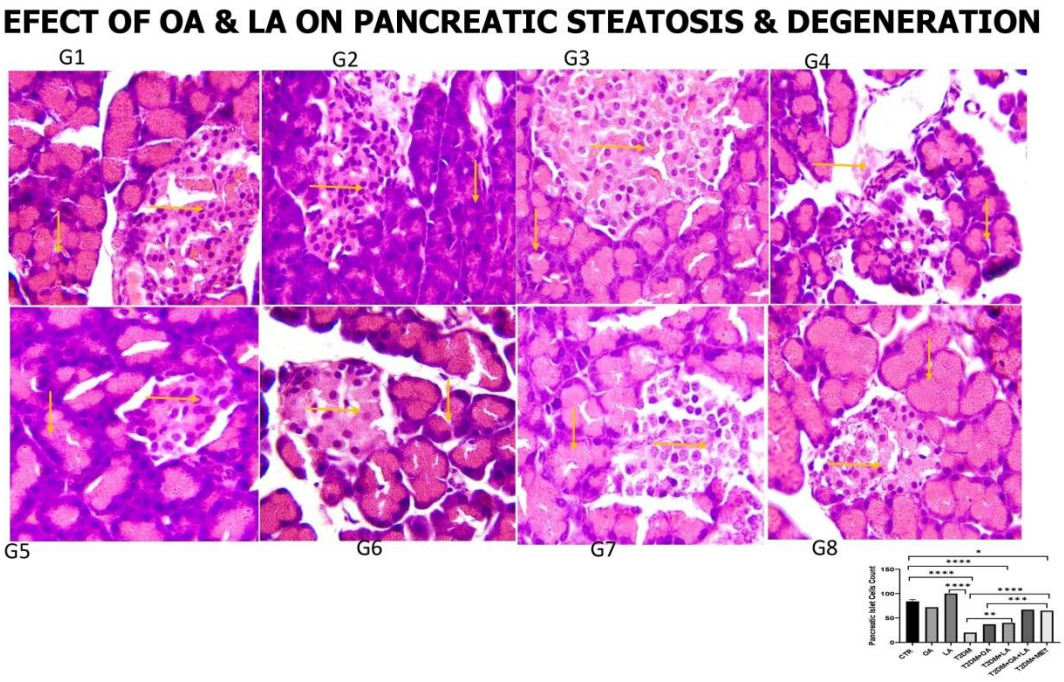


Figure 6: H&E-stained pancreas section showing pancreatic degeneration, steatosis among the experimental groups. G1: normal control (CTR), GP2: oleic acid only (OA), G3: linoleic acid only (LA), G4: diabetic control (T2DM), G5: oleic Group (T2DM+OA), G6: linoleic acid treatment group (T2DM+LA), G7: oleic & linoleic acid combined treatment group (T2DM+OA+LA) and G8: metformin treated group (T2DM+MET) (Mag. x800).