EJPMR, 2026, 13(8), 315-323 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

THE HISTOLOGICAL AND BIOCHEMICAL EFFECTS OF THE N-HEXANE FRACTION OF *TELFAIRIA OCCIDENTALIS* LEAVES ON THE LIVER OF STREPTOZOTOCIN-INDUCED DIABETIC WISTAR RATS

Arayombo Babatunde E.*, Adewole Stephen O., Solomon Abolade A.

Department of Anatomy and Cell Biology, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria.

***Corresponding Author: Arayombo Babatunde E.**

Department of Anatomy and Cell Biology, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria. DOI: https://doi.org/10.5281/zenodo.21702538

How to cite this Article: Arayombo Babatunde E.*, Adewole Stephen O., Solomon Abolade A., (2026). The Histological and Biochemical Effects Of The N-Hexane Fraction of *Telfairia Occidentalis* Leaves On The Liver Of Streptozotocin-Induced Diabetic Wistar Rats. European Journal of Pharmaceutical and Medical Research, 13(8), 315–323.

Article Received on 26/06/2026 **Article Revised on 17/07/2026** **Article Published on 01/08/2026**

ABSTRACT

Introduction: DM is a metabolic disorder that not only impairs pancreatic function but also disrupts liver protein balance and compromises hepatic structural integrity. **Aim:** To assess the effect of the n-hexane fractions of TO (nHFTO) leaves extracts on liver injury caused by DM. **Methodology:** Thirty-six adults male Wistar rats weighing between 190-200g were randomly assigned to six groups (1-6) of six rats each. All rats were fed high fat rat diet for 4 weeks and given free access to water. Group 1 received 2 mL/kg of distilled water orally for 28 days. DM was induced in groups 2-6 by the intraperitoneal administration of STZ 45mg/kg for 5 days and 24 hours after STZ, rats in group 2 were sacrificed. Groups 3, 4 and 5 were treated with nHFTO 20, 40, 60 mg/kg/day, respectively for 28 days. Group 6 was treated with (Humulin 70:30) Insulin 5 IU/kg/day subcutaneously for 28 days. Following the completion of STZ, nHFTO, and insulin treatments, animals in group 3 – 6 were allowed a 2-week *washout period*. At the end of the experiment, the animals were sacrificed, liver was harvested and fixed in 10% formol saline for histological processing. The blood samples were collected by cardiac puncture to assay for Alanine aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-Glutamyl transferase (GGT), Packed cell volume (PCV), albumin, bilirubin and total protein. **Conclusion:** nHFTO treatment produced a dose-dependent hepatoprotection, antihyperglycemic effects and hematological restoration against STZ-induced DM. highest dose of nHFTO showed optimal activity in effects compared to the standard drug.

KEYWORD: Streptozotocin, liver, Insulin, nHFTO.

1. INTRODUCTION

Medicinal plants have gained increasing attention in diabetes management due to their therapeutic potential and comparatively lower incidence of adverse effects than conventional drugs. Evidence suggests that a high habitual intake of flavonoids from fruits and vegetables during adolescence may reduce the risk of developing type 2 diabetes–related factors in early adulthood (Rodríguez et al., 2018).

Telfairia occidentalis (fluted gourd or pumpkin), a flavonoid-rich plant, is widely cultivated across several West African regions, particularly in Sierra Leone and parts of Nigeria, for both nutritional and medicinal purposes. Its leaves and seeds are the most commonly consumed components, serving as vegetables and sources of edible oil, respectively (Salman et al., 2021). Pharmacological studies have reported that Telfairia occidentalis (T.O.) exhibits diverse biological activities, including hypoglycaemic, antiplasmodial, antihypertensive, anti-anaemic, anti-inflammatory, and antioxidant effects, with its hypoglycaemic potential being especially well established (Salman et al., 2021).

DM is defined as 'a metabolic disease caused by the inability of pancreas to make insulin (insulin deficit) or properly use the insulin released (insulin resistance), or both, which can be caused by oxidative and inflammatory stress, among other things' (Akpotu et al., 2022). Over half a billion people are currently living with diabetes worldwide, representing more than 10.5% of the global adult population. This growing prevalence has imposed a substantial economic burden, with global diabetes-related health expenditures estimated at USD

966 billion in 2021 and projected to rise to USD 1.054 trillion by 2045 (Sun et al., 2021). In Africa, there are 25 million cases of *people living with diabetes* (PLWD) which is forecasted to rise towards 60 million by 2045. In Nigeria, an estimate of 3 million PLWD was reported (IDF, 2026).

Manifestation of prolonged high blood glucose leads to sign and symptoms of diabetes-specific non-alcoholic fatty liver disease, kidney, eye and peripheral nerve disorders consequently leading to hepatopathy, nephropathy, retinopathy and peripheral neuropathy" (Arayombo et al., 2024). DM is associated with a number of liver abnormalities, such as abnormal glycogen deposition, nonalcoholic fatty liver disease (NAFLD), fibrosis, cirrhosis, hepatocellular carcinomas (HCCs), abnormal elevated hepatic enzymes, acute liver disease and hepatitis (Arayombo et al., 2024).

The onset of diabetes in the liver is associated with biochemical and functional abnormalities, including oxidative stress and apoptosis, which subsequently promote inflammatory responses and pathological changes such as necrosis or fibrosis, commonly observed in the progression of nonalcoholic fatty liver disease (Rodríguez et al., 2018).

Several precautionary measures have been put in place to ensure that the elevated liver enzymes seen in this research emanated from diabetic influence rather than STZ as discussed in the methodology. The molecular mechanisms underlying the link between insulin signaling and hepatocellular injury are only partly understood (Kohl et al., 2013). Therefore, this study is aimed at assessing the effect of the n-hexane fractions of TO leaves extracts on liver injury caused by DM.

2. MATERIALS AND METHODS

2.1 Extraction of n hexane fraction of *Tefairia occidentalis*

2.1.1 Preparation of Sample

Fresh TO leaves were removed from the stem, washed in distilled water, air-dried at room temperature, weighed at intervals to obtain a stable weight to ensure proper dryness, and then pulverized with a mechanical blender.

2.1.2 Procedure for Solvent Extraction

Pulverized TO leaves were soaked in n-hexane, in a ratio of 1:3 (w/w); the mixture was intermittently agitated with magnetic stirrer and shaken. For better efficiency, a mixture of solvents n-hexane:acetone:ethanol (5:4:1) were used to break down the matrix. The extraction was carried out at 40°C for 60 minutes. The mixture was centrifuged and then filtered with Whatman's paper no 1 to separate the solid residue from the solvent phase.

2.1.3 Fractionation and Purification

The extract was transferred to a separating funnel and distilled water was added in enhancing the phase separation to allow the lipophilic n-hexane to separate from the aqueous layer. The n-hexane layer was then washed in distilled water to remove impurities. The extract was dried using anhydrous sodium sulfate to remove remaining traces of water.

The n-hexane fraction was concentrated using a rotary evaporator at 40°C under low pressure to obtain a concentrated extract in a hood to a small volume, for higher purity fraction, ethanol was added to the concentrated extract as an anti-solvent at low temperatures (0°- 4°C) to precipitate the TO n-hexane fraction. The resulting crystals were collected by vacuum filtration, dried and kept at low temperatures (-40°C), in the dark.

$$\text{Yield} = \frac{\text{Weight of n-hexane - free extract of TO (g)}}{\text{Weight of TO leaves (g)}}$$

(Kalpana and Manisha, 2015).

Data generated were analyzed by using descriptive and inferential statistics. *GraphPad prism version 8.4.3.686* was employed.

2.2 Streptozotocin preparation

STZ was prepared following the methods recommended by Ghasemi and Jeddi (2023). STZ solution was prepared and maintained in 0.1M ice-cold acidic (pH 4.5) citrate buffer, and was used immediately after its preparation. To prevent degradation due to its photosensitivity, STZ was prepared in tube wrapped with aluminum foil.

2.3 Induction of diabetes

DM was induced in overnight-fasted Wistar rats through a five-day series of low dose intraperitoneal injection of STZ (45 mg/kg) dissolved in citrate buffer. To prevent acute hypoglycemia caused by STZ-induced β-cell dysfunction, the animals were provided with 5% dextrose water *ad libitum*, 24 hours post STZ administration. This method is consistent with the method of Ghasemi and Jeddi (2023).

2.4 Experimental design

Ethical clearance for the study was obtained from health research ethics committee (HREC), institute of public health (IPH) Obafemi Awolowo University (OAU) Ile-Ife. The animals were given humane care according to the guidelines of HREC, IPH, OAU.

Thirty-six adults male Wistar rats weighing between 190-200g were used for this study. The rats were randomly assigned to six groups (1-6) of six rats each. All rats were fed high fat rat diet for 4 weeks and given free access to water, kept and maintained under standard laboratory conditions.

Group 1 (normal control) received 2ml/kg/day of distilled water orally for 28 days. DM was induced in groups 2-6 by the intraperitoneal administration of STZ 45mg/kg for 5 days and 24 hours after STZ, rats in group 2 were sacrificed. Groups 3, 4 and 5 were treated with nHFTO 20, 40, 60 mg/kg/day, respectively for 28 days.

Group 6 was treated with (Humulin 70:30) Insulin 5 IU/kg/day subcutaneously for 28 days. Following the completion of STZ, nHFTO, and insulin treatments, animals in group 3 – 6 were allowed a 2-week *washout period*

At the end of the experiment, the animals were sacrificed by cervical dislocation, liver was harvested and fixed in 10% formol saline for histological processing. The blood samples were collected by cardiac puncture into plain bottle for the serum analysis to assay for Alanine aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-Glutamyl transferase (GGT), Packed cell volume (PCV), albumin, bilirubin and total protein.

2.5 Random blood sugar record

The rats were sampled in the caudal tail vein to measure the RBS level in the blood. All the measurements were done with a glucometer. Before sampling, a tail was rubbed by gently massaging a peripheral blood flow, disinfected using an alcohol swab before being punctured with a lancet. The first droplet was discarded and the second droplet put on a glucose test strip to be examined. All readings were recorded properly and rats with blood glucose levels above 215 mg/dL (11.1 mmol/L) were considered diabetic.

3 RESULTS

3.1 Biochemical evaluations

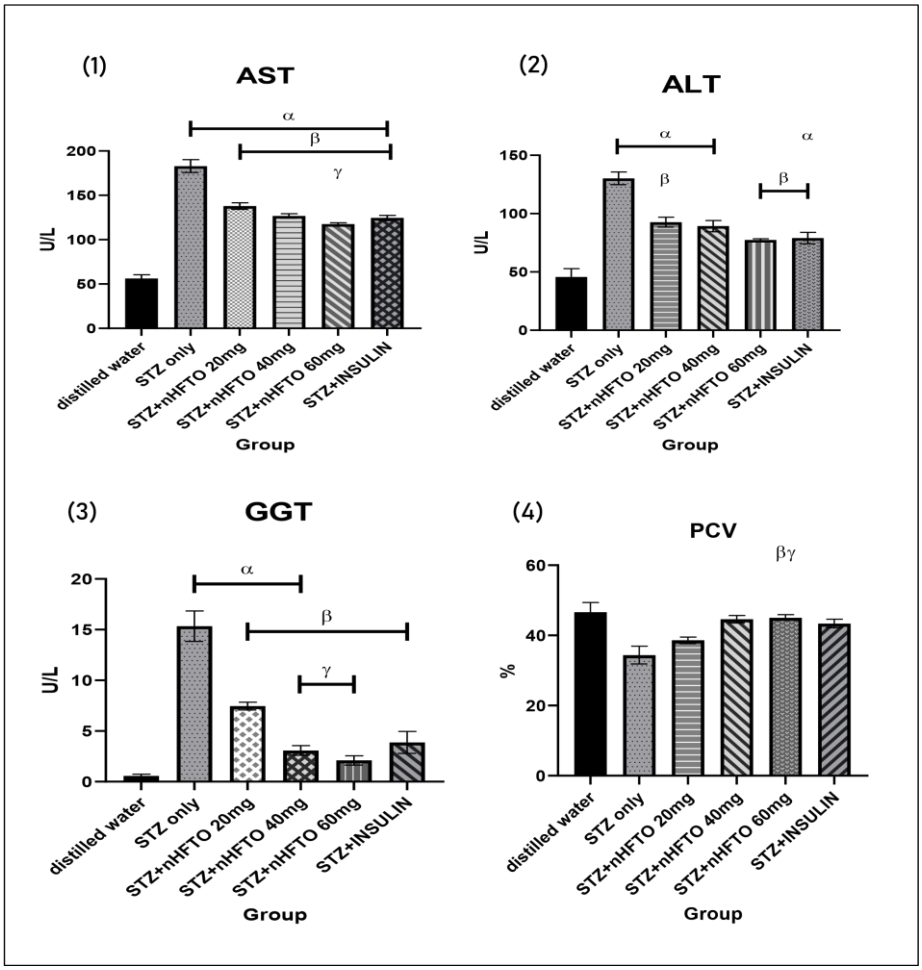


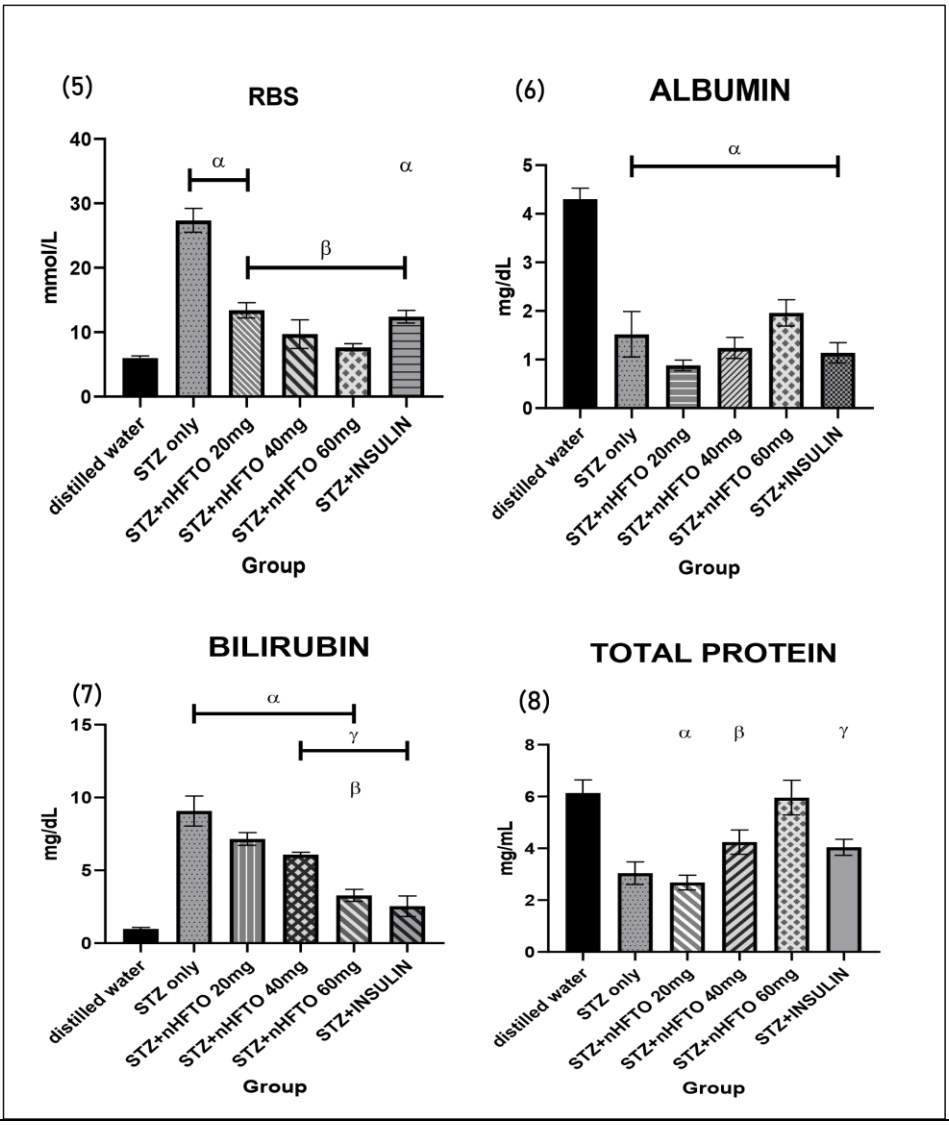
Figure (1) showed the effect of nHFTO on the AST concentration in liver of STZ-induced DM in adult male Wistar rats. Statistically there was a significant reduction in AST concentration in groups 2 – 6 when compared to group 1 ($p<0.05$). The interventions provided to groups 3, 4, 5 and 6 reduced the concentration of AST significantly when compared to group 2; and the effects of nHFTO were dose dependent with nHFTO 60 mg showing the highest efficacy when compared to the lowest dose ($p<0.05$). Statistically there was no significant difference between insulin treated group and nHFTO treated groups ($p>0.05$).

Figure (2) showed the effect of nHFTO on the ALT concentration in liver of STZ-induced T2DM in adult male Wistar rats. There was a marginal rise in ALT concentration of rats treated with STZ, meanwhile when compared to group 1, there was a significant rise in ALT concentration in groups 2, 3, 4 and 6 ($p<0.05$). nHFTO 20mg, 60 mg and INSULIN 5 IU/kg reduced ALT concentration significantly when compared to groups 2,

indicating ameliorative effect of nHFTO on liver injury ($p<0.05$). There was no significant difference in ALT levels between nHFTO treated groups and INSULIN treated group ($p>0.05$).

Figure (3) showed the effect of nHFTO on the GGT concentration in liver of STZ-induced DM in adult male Wistar rats. The graph showed a rise in the GGT concentration of rats treated with STZ. There was significant rise in GGT concentration of groups 2, 3 and 4 when compared with group 1; however, the provision of interventions reduced GGT concentration in groups 2-6, and statistically this was found significant ($p<0.05$). There was no significant difference in nHFTO levels between the nHFTO treated and INSULIN treated rats, whereas the effect of nHFTO was found dose-dependent (20mg>40mg&60mg) ($p>0.05$).

Figure (4) showed the effect of nHFTO on the PCV in adult male Wistar rats with STZ-induced DM. A reduction in PCV was observed in groups 2 and 3 when compared to group 1, however this was found statistically insignificant ($p>0.05$). nHFTO 60 mg improved PCV significantly in group 5 when compared to the group 2 treated with STZ only and the group 3 treated with STZ+nHFTO 20mg. Statistically there is no significant difference in PCV nHFTO treated groups and INSULIN treated group ($p>0.05$).



*Data were expressed as mean ± SEM. '**α**' is significantly different from group 1, '**β**' is significantly different from group 2 and '**γ**' is significantly different from group 3.*

Figure (5) showed the effect of nHFTO on the RBS in adult male Wistar rats with STZ-induced T2DM. RBS concentration spiked up in groups treated with STZ, however a significant rise in RBS level was found in groups 2, 3 and 6 when compared to group 1 ($p<0.05$). The intervening agents (Nhfto & INSULIN) reduced RBS level drastically in groups 3 -6 compared to group 2; and statistically there was no difference between groups treated with nHFTO and INSULIN ($p>0.05$)

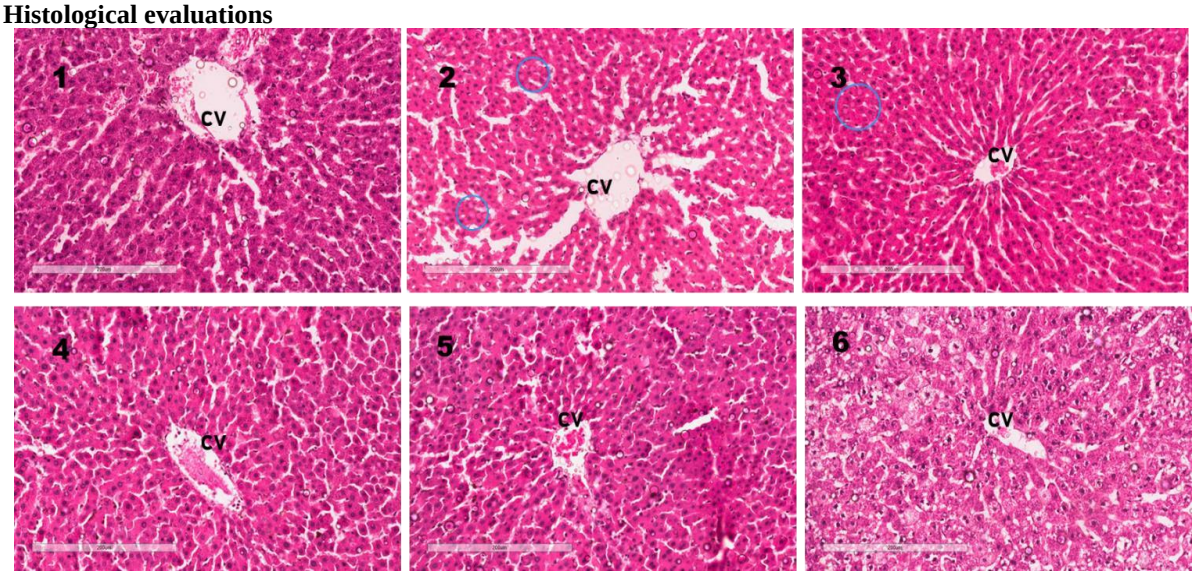
Figure (6) showed the effect of nHFTO on the albumin levels in liver of STZ-induced T2DM in adult male

Wistar rats. There was a significant reduction in albumin level in groups 2 - 6 when compared with group 1. The interventions provided did not restore albumin level to normal, and no significant differences were observed among the experimental groups ($p>0.05$).

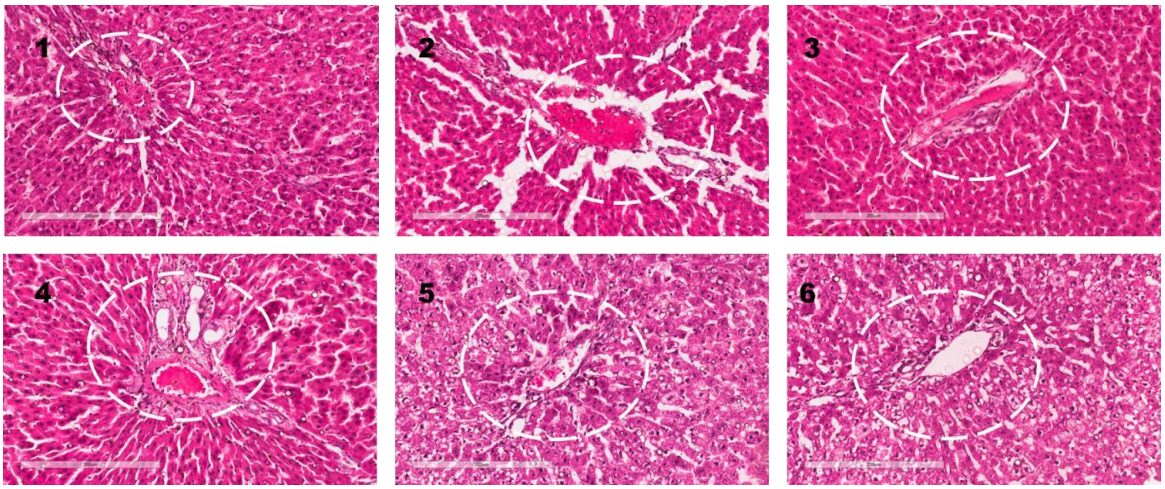
Figure (7) showed the effect of nHFTO on the bilirubin levels in liver of STZ-induced T2DM in adult male Wistar rats. There was a rise in bilirubin levels in the experimental groups 2-6. Statistically the rise in bilirubin levels in groups 2-5 was found significantly different from group 1. the graph showed that medium dose, high dose of nHFTO and INSULIN reduced bilirubin levels more effectively when compared to the low dose of nHFTO, and the difference in effect was found statistically significant ($p<0.05$).

Figure (8) showed the effect of nHFTO on the total protein in liver of STZ-induced T2DM in adult male Wistar rats. There was a reduction in levels of total proteins for rats treated with STZ; however, the total protein level was found to be within normal range in the rats treated with nHFTO 40 mg/kg, 60 mg/kg and INSULIN 5 I/U/kg.

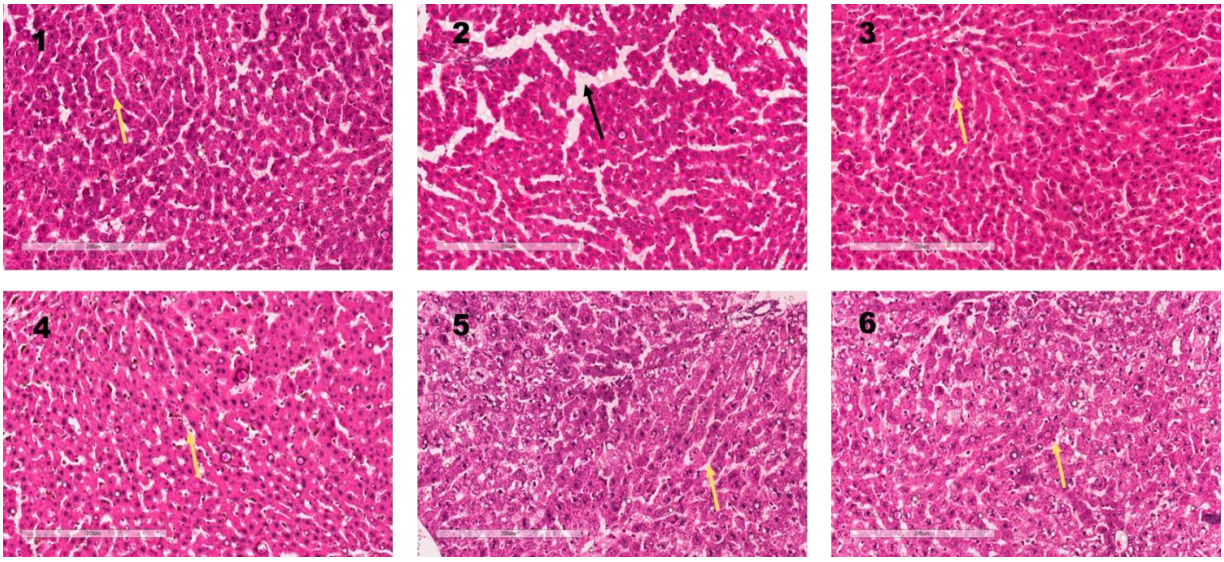
3.2 Histological evaluations



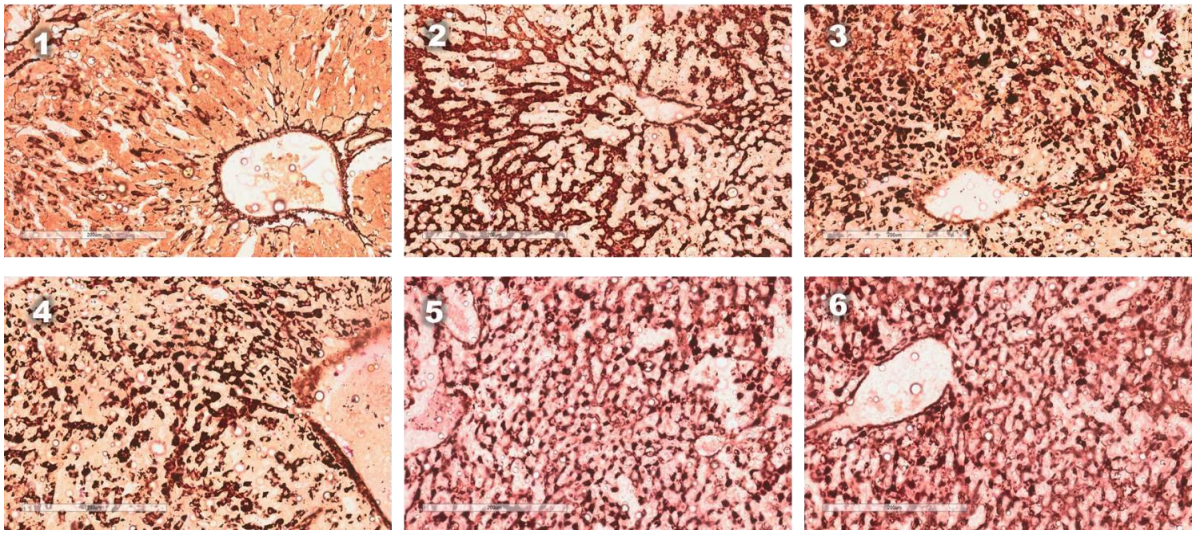
Representative photomicrographs of 1-6 showing liver histoarchitecture (Zone 3).
Group 1 showed hepatocytes arranged in an orderly and normal hepatic architecture with an organized hepatic cell cords radiating from the central vein, whereas the diabetic group (2) showed dilated sinusoids and disorderly arranged hepatocyte characterized with highly eosinophilic cytoplasm (eosinophilic foci) indicating inflammation and some cytoplasmic inclusions (blue circle). However, a progressive restoration of hepatic histoarchitecture was seen in groups provided with interventions (3-6). H and E X200.



Representative photomicrographs of 1-6 showing the liver histoarchitecture (Zone 1). *Photomicrograph 1 showed normal histoarchitecture of the liver with its portal triads (white circle). The diabetic group (2) showed disordered hepatocyte histoarchitecture with presence of dilated sinusoids. However, a restoration of hepatic histoarchitecture was seen in groups provided with interventions (3-6). H and E X200.*



Representative photomicrographs of 1-6 showing the liver histoarchitecture (Zone 2).
Photomicrograph 1 showed the normal histoarchitecture of the liver with an organized hepatic cell cord and normal sinusoid diameter (orange arrow), however, there is a dilation of sinusoids (black arrow) in the diabetic group (2) and a disarrangement of hepatic cords. The interventions provided restored liver histoarchitecture in groups (3-6). H and E X200.



Representative photomicrographs of 1-6 showing the liver histoarchitecture.
Photomicrograph 1 displays the normal liver architecture with a typical, delicate pattern of reticulin fibers (black). In the diabetic group (2), chronic hyperglycemia led to noticeable thickening of these fibers. In contrast, the intervention groups (3–6) demonstrated signs of structural recovery, shown by the reduction in reticulin fiber staining. Reticulin sliver stain X200

4 DISCUSSION

Streptozotocin (STZ) is widely known for its selective pancreatic β-cell toxicity, resulting in insulin deficiency, persistent hyperglycemia, and secondary metabolic disturbances. In this study, STZ administration produced significant alterations in liver histoarchitecture and also hepatic biochemical markers, hematological parameters, and protein profiles, confirming successful induction of DM in adult male Wistar rats.

The marked elevation of serum transaminases ALT, AST, and GGT (figure 1-3) in the untreated diabetic rats (STZ-only group) is consistent with diabetes-induced hepatic injury (Bae & Ahn, 2022). Chronic hyperglycemia promotes oxidative stress, lipid peroxidation, and structural damage to hepatocytes, leading to increased leakage of transaminases into the systemic circulation (Al-Attar & Alsalmi, 2019). Treatment with nHFTO significantly reduced these liver enzyme levels in a dose-dependent pattern, with the 60 mg/kg dose showing the greatest attenuation and often approaching the effect of insulin-treated animals. This suggests that nHFTO mitigates hepatocellular membrane damage likely

through its antioxidant capabilities. The presence of bioactive chemicals such as flavonoids, alkaloids, and terpenoids documented in TO has been linked with this therapeutic benefit. The hepatoprotective effect of TO is consistent with previous reports that extracts of TO preserve hepatic architecture and reduce serum transaminases in rats with induced liver injury (Oladele, 2017; Seyifunmi & Ajayi, 2020).

Figure (5) showed that STZ-induced T2DM produced the expected significant elevation in RBS levels. Hyperglycemia persisted throughout the study in the untreated diabetic group. Administration of nHFTO resulted in a dose-related fall in blood glucose levels, with nHFTO 60 mg/kg demonstrating the most substantial reduction. This antihyperglycemic activity may be attributed to: improved residual β-cell function, enhanced peripheral glucose uptake, possible insulin-mimetic or insulin-sensitizing mechanisms and the inhibition of glucose absorption or hepatic gluconeogenesis (Alam et al, 2022; Arayombo et al., 2024). The glycemic improvement seen in the nHFTO-treated groups and the close similarity with the insulin-treated group further highlight the therapeutic potential of the nHFTO in DM.

The in group 2 aligns with reports that chronic hyperglycemia impairs erythropoiesis due to oxidative stress, dehydration, glycation of hemoglobin, and possible hemolysis. nHFTO treatment significantly restored PCV toward normal values. This suggests improved erythropoietic activity or stabilization of red blood cell membranes, likely due to antioxidant phytochemicals that counter oxidative damage. The highest dose again produced the greatest normalization, showing that nHFTO may combat the anemia associated with uncontrolled diabetes.

Chronic hyperglycemia is known to disrupt liver synthetic function, leading to reductions in albumin synthesis and total protein levels, and elevation of bilirubin; reflecting impaired protein synthesis and hepatobiliary dysfunction (Ghanbari et al., 2016). Findings reveal low albumin and total protein in diabetic rats and elevated bilirubin, suggesting hepatic stress or reduced conjugation (Williams et al., 2023). Nevertheless, the treatment with nHFTO reversed these abnormalities in a graded manner. The improvement in protein parameters indicated restoration of hepatic synthetic ability, while the reduction in bilirubin suggests enhanced liver detoxification and improved integrity of hepatocytes. The similarity between the highest nHFTO dose (60 mg/kg) and the insulin-treated group further demonstrates the potency of the n-hexane fraction in preserving liver function and structure.

The changes in these biochemical markers (ALT, AST, GGT, bilirubin, albumin, and total protein) has been linked with alterations in structural integrity of the liver (Thakur et al., 2024). Histological examination of rats induced with DM revealed disruptions of hepatic strands, mild hepatocellular necrosis, highly eosinophilic cytoplasm indicating lymphocytic infiltration (Inflammation), along with the presence of cytoplasmic inclusions. Insulin and nHFTO restored tissue integrity, however the improvement observed in nHFTO treated groups appeared dose-dependent, with the lowest dose producing the least effect (cytoplasmic inclusion prominent).

The reticulin silver stain showed a clear structural alteration caused by chronic hyperglycemia. The diabetic groups (2-6) showed marked thickening and distortion of reticulin fibers, consistent with chronic hyperglycemia–induced extracellular matrix remodeling as reported by many studies (Khan *et al*., 2025; Xiong *et al*., 2025). Meanwhile, tissue repair was observed in the groups treated with nHFTO and INSULIN evident by a reduction in reticulin deposition as seen in plate 4.

This extracellular matrix remodeling seen in DM has been linked with 'longer diabetes duration, insulin resistance, and microalbuminuria' (Martínez-Sánchez et al., 2025). Khan et al. (2025) reported that 'chronic hyperglycemia and insulin resistance promote ECM remodeling through oxidative stress, inflammatory cytokines, and advanced glycation end products (AGEs), leading to fibrosis, vascular dysfunction, and impaired tissue repair'. The progressive reduction in reticulin deposition observed in group 3 - 6, indicate partial restoration of hepatic architecture, suggesting that the administered treatments (nHFTO and INSULIN) mitigated the fibrotic changes caused by DM, likely as a result of the restoration of altered liver biomarkers towards normal and their hypoglycemic effect.

These findings confirm the ameliorative effect of nHFTO on the injury induced by chronic hyperglycemia on hepatocytes and also support the traditional use of TO in managing metabolic conditions, highlighting the potential of its n-hexane fraction as a therapeutic alternative for diabetes-associated hepatic dysfunction.

In conclusion, nHFTO treatment produced a dose-dependent hepatoprotection, antihyperglycemic effects and hematological restoration against STZ-induced DM. highest dose of nHFTO showed optimal activity in effects compared to the standard drug.

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