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Article

Metabolic Responses of BALB/c Mice to a Short-Term Fructose Feeding via Drinking Water – a Preliminary Report

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Abstract

Excessive fructose consumption has been linked to metabolic dysregulation and liver injury, particularly Metabolic-Dysfunction Associated Steatotic Liver Disease (MASLD). However, there remains insufficient information on the early-stage metabolic and hepatic responses to fructose, especially in BALB/c mice. This preliminary study was designed to evaluate the metabolic and hepatic tissue responses of BALB/c mice to graded fructose intake via drinking water. BALB/c mice (18) were randomly divided into control, 20% fructose and 30% fructose groups. Mice were provided *ad libitum* access to a diet and drinking water containing 0%, 20% or 30% fructose. All treatments lasted for twenty-one (21) days, during which body weights were monitored weekly. Plasma glucose, insulin, lipids and liver function indices were quantified in the plasma. Additionally, biomarkers of oxidative stress and inflammation were assessed in liver homogenates. Liver sections from the various groups were fixed in neutral buffered formalin and subjected to histopathological examination after hematoxylin and eosin staining. Fructose intake for 21 days induced significant weight gain in mice administered 30% fructose relative to the control group. Total cholesterol and triglyceride levels increased significantly ($p < 0.05$) in fructose-treated mice compared with the control. There was also a significant increase ($p < 0.05$) in the oxidative stress biomarker (malondialdehyde, MDA) level, followed by a significant decrease in levels/activities of hepatic antioxidants (Reduced Glutathione (GSH), Glutathione peroxidase (GSH-Px), Superoxide Dismutase (SOD) and Catalase, CAT). Additionally, the level of nitric oxide (NO) and TNF-α increased in liver homogenate relative to the control, followed by an increase in plasma hepatic biomarkers (ALT and AST). The control group showed a normal liver histological pattern, while mice administered 20% fructose showed mild hepatic histological alterations. In contrast, 30% fructose administration induced more pronounced hepatic injury characterised by moderate centrilobular congestion, inflammatory cell infiltration within portal regions, and microvesicular steatosis. Fructose consumption via drinking water induces dose-dependent metabolic and hepatic alterations in BALB/c mice, with higher concentrations promoting steatosis, inflammation, and early features of hepatocellular injury. These findings support the role of high dietary fructose in the onset of metabolic liver dysfunction and provide a foundation for further investigation into underlying molecular mechanisms.

Keywords: Fructose, Metabolic dysregulation, Hepatic steatosis, Oxidative stress, Liver injury

Abbreviations

CAT, catalase; ChREBP, carbohydrate-responsive element-binding protein; DNL, De novo lipogenesis; ER, endoplasmic reticulum; FFAs, free fatty acids; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; H&E, hematoxylin and eosin; HOMA-IR, homeostatic model assessment for insulin resistance; IL-6, Interleukin-6; INS, insulin; LPS, lipopolysaccharide; MASLD, metabolic-dysfunction associated steatotic liver disease; MDA, malondialdehyde; NAFLD, Non-alcoholic fatty liver

disease; NBF, neutral buffered formalin; NO, nitric oxide; PBS, phosphate-buffered saline; ROS, Reactive oxygen species; SD, standard deviation; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element-binding protein 1c; TC, total cholesterol; TG, triglycerides; TNF-α, Tumour necrosis factor alpha

1. Introduction

The non-alcoholic fatty liver disease (NAFLD), currently referred to as metabolic-dysfunction associated steatotic liver disease (MASLD), is considered to be a major global health concern, and is closely linked to insulin resistance, type 2 diabetes mellitus and obesity (Targher et al. 2025). The prevalence of MASLD has increased significantly over the years, due to changes in dietary habits, especially increased intake of fat-rich and fructose-rich diets (Miao et al., 2024). Dietary fructose has been identified as a major contributor to the development of hepatic steatosis (Lujan et al., 2026).

Fructose metabolism (or fructolysis, Figure 1) occurs in the liver, in a metabolic process that allows uncontrolled substrate flow into lipid-synthesising pathways (Muriel et al., 2021). Consequently, increased de novo lipogenesis (DNL) occurs in the liver, resulting in fat deposition in hepatocytes (a key feature of MASLD) (Geidl-Flueck et al., 2023). Moreover, fructose metabolism is linked to ATP depletion, increased uric acid production, and mitochondrial dysfunction, contributing to oxidative stress and inflammation that ultimately drive the progression from steatosis to steatohepatitis (Caliceti et al., 2017).

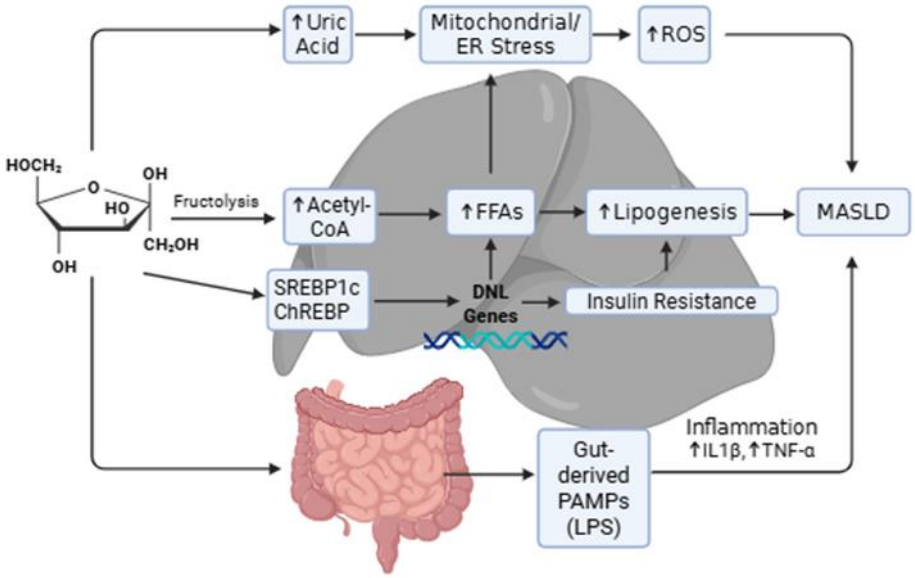

Figure 1: Fructose metabolism and the pathogenesis of MASLD

Various experimental models have demonstrated the capacity of fructose to induce characteristic symptoms of MASLD, including liver fat deposition, inflammation, insulin resistance, and metabolic abnormalities (Spruss et al., 2009; Mamikutty et al., 2015; Todoric et al., 2020; Bhattacharjee et al., 2025). Fructose feeding in rodents has been increasingly employed as a model of human exposure to sugar-sweetened beverages (Mamikutty et al., 2015; Softic et al., 2017). Fructose not only acts as a lipid precursor but also acts as an activator of lipogenic transcription factors such as the carbohydrate-responsive element-binding protein, and sterol regulatory element-binding protein 1c, enhancing fatty acids and triglycerides biosynthesis (Jung et al., 2022; Baharuddin, 2025). In addition to promoting lipogenesis, fructose has been shown to impair fatty acid oxidation and increase oxidative stress, thereby contributing to hepatic injury (Inci et al., 2023).

Previous studies have demonstrated that fructose administration via drinking water can rapidly induce hepatic DNL, mitochondrial dysfunction, and reactive oxygen species (ROS) generation, even over short exposure periods, highlighting its potent metabolic impact (Spruss et al., 2009; Mamikutty et al., 2015). Although there is evidence supporting the role of fructose in the pathogenesis of MASLD, a number of variations remain depending on experimental conditions such as fructose concentration,

duration of exposure, and animal strain. Several studies have utilised C57BL/6 mice due to their susceptibility to diet-induced obesity and metabolic dysfunction, while other studies used various rat strains. However, relatively few studies have explored fructose-induced metabolic responses in BALB/c mice. This limits the generalizability of findings and underscores the need for strain-specific studies.

Additionally, the administration of fructose via drinking water is particularly relevant, as it closely mimics human patterns of sugar intake, particularly through beverages (Herman & Birnbaum, 2021). However, differences in voluntary intake, metabolic adaptation, and strain-specific susceptibility necessitate careful evaluation of this model, especially in less commonly studied strains such as BALB/c mice. Consequently, this study was designed to investigate the metabolic responses of BALB/c mice to fructose feeding via drinking water, with particular emphasis on early metabolic alterations associated with MASLD. As a preliminary report, this study seeks to contribute to the growing body of evidence on fructose-induced metabolic dysfunction and to provide insights into the suitability of BALB/c mice as a model for fructose-driven MASLD pathology.

2. Materials and Methods

2.1 Assay Kits and Chemicals

Assay kits for glucose, ALT, AST, total cholesterol and triglycerides were products of Fortress Diagnostics (Antrim, UK). ELISA kits for mouse TNF-α and INS were procured from Elabscience (Houston, TX). Fructose was purchased from Macklin Inc., Shanghai, China. Other reagents used in this study were of research grade.

2.2 Study design

Eighteen male BALB/c mice (6-7 weeks old; 20-23 g) were utilised for this study. After one week of adaptation to standard housing conditions, the mice were randomly assigned to control, 20% fructose, and 30% fructose groups. The mice had free access to food and drinking water containing 0%, 20%, or 30% fructose, respectively. All treatments lasted for twenty-one (21) days, during which body weights were recorded weekly. Ethical approval was granted by the Ethical Review Committee of the Faculty of Natural Sciences, Ajayi Crowther University, Oyo (FNS/ERC/2025/018FNF).

2.3 Sample Collection and Processing

After twenty-one days of treatment, mice were fasted for 12 hours and sacrificed. Blood samples were obtained via the retro-orbital vein. Samples were collected into both fluoride oxalate-coated tubes (for glucose analysis) and Li-heparin tubes for other assays. Plasma was prepared by subjecting blood samples to 4000 rpm for 5 minutes. Liver samples were rinsed in ice-cold PBS (pH 7.4), blotted to dry and weighed for preparation of liver homogenates. Liver sections were fixed in 10% NBF and subsequently used for histopathology. Liver samples were minced and homogenised in PBS to prepare a 10% w/v homogenate. The homogenate was centrifuged at 10,000 ×*g* for 10 minutes at 4°C. Supernatants collected were stored at -20°C. Protein concentration in liver homogenate was assayed by the biuret method (Gornall et al., 1949).

2.4 Biochemical Analyses

Glucose concentration, activities of the liver enzymes ALT and AST, and levels of TC and TGs were quantified using assay kits based on the manufacturer's specified procedures. Hepatic levels of reduced GSH and glutathione peroxidase (GSH-Px) activity were measured according to the method of Jollow et al. (1974) and Gross et al. (1967), respectively. The hepatic MDA level was quantified according to Varshney and Kale (1990). Nitric oxide concentration was quantified based on the method described by Green et al. (1982). The concentrations of plasma insulin and hepatic TNF-α were quantified based on the Sandwich-ELISA principle following the manufacturer's procedure. Insulin resistance index was calculated using the homeostasis model assessment (Matthews et al., 1985).

2.5 Histopathology

Liver sections fixed in 10% neutral buffered formalin (NBF) were dehydrated in ethanol and embedded in paraffin wax. Thin sections (5 μm in thickness) were stained with H&E and evaluated for morphological alterations.

2.6 Statistical analysis

Data were analysed by one-way ANOVA and complemented with Tukey's test. *P* values <.05 were considered significant. Data were presented as mean ± SD.

3. Results

3.1 Influence of fructose consumption on glucose, insulin and body weight gain

The two doses of fructose administered caused a significant increase in plasma glucose level compared with the control (Figure 2). Similarly, there was a significant increase *(P<0.05)* in plasma insulin levels, followed by a significant increase in the insulin resistance index. There was an increase in weight gain in the groups administered fructose compared with the control. However, when compared with the control group, only the 30% fructose group showed a statistically significant increase in body weight.

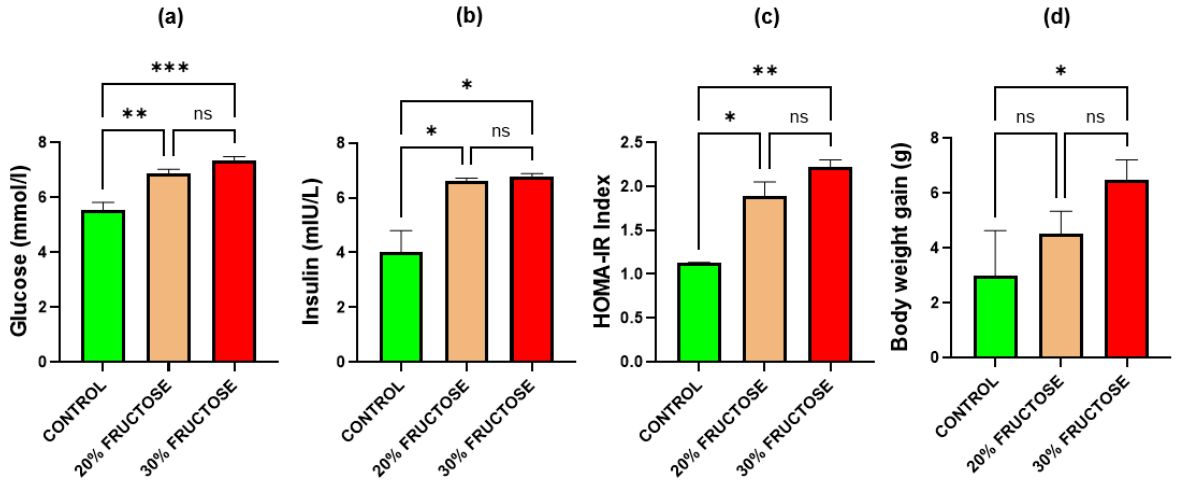

Figure 2: Effect of fructose consumption on (a) plasma glucose, (b) plasma insulin concentration, (c) insulin resistance index and (d) body weight in BALB/c mice. **Statistically significant (P<0.05), ns, not statistically significant*. $HOMA - IR = [Insulin\ (mIU/L) \times Glucose\ (mmol/L)]/22.4$.

3.2 effects of fructose consumption on plasma and hepatic lipids

Figure 3 shows the effects of fructose consumption for twenty-one days on plasma and hepatic total cholesterol and triglycerides. There was a significant increase in plasma and hepatic levels of total cholesterol in 30% fructose-fed mice compared with control. However, the increase in cholesterol level was not statistically significant in the 20% fructose group compared with control. In the fructose group, there was a significant increase in plasma triglycerides levels compared with triglycerides levels in the control group. However, while the level of triglyceride increased in the liver of mice fed with fructose, only the 30% group showed a statistically significant increase compared with the control.

3.3. Effect of fructose on hepatic markers of inflammation

Figure 4 shows the influence of fructose consumption on biomarkers of inflammation (NO and TNF-α) in the liver of mice. The level of NO increased in the liver homogenates of fructose-fed mice; however, only the 30% fructose group showed a statistically significant difference in NO level,

compared with the control. Similarly, the plasma concentration of TNF-α increased significantly in the 30% fructose-fed mice compared with the controls.

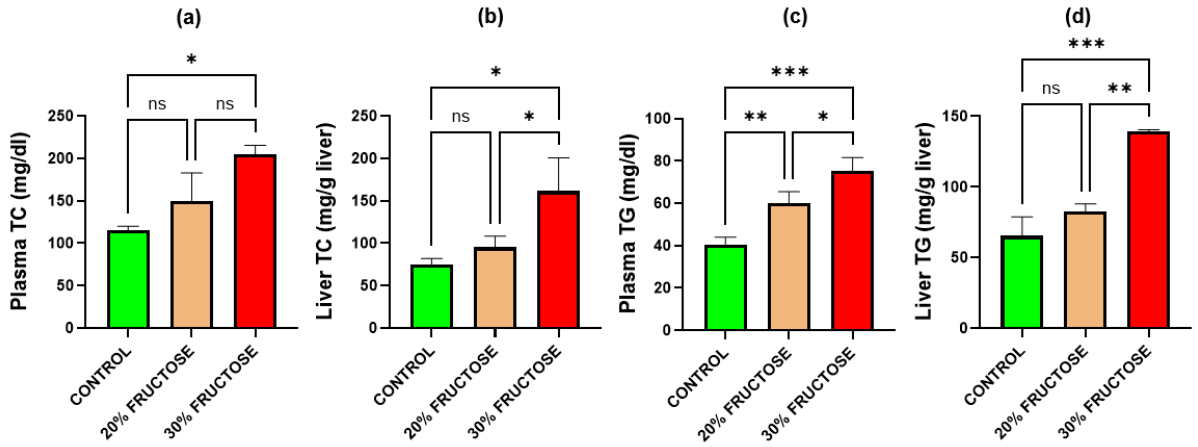

Figure 3: Effect of fructose consumption on (a) plasma total cholesterol, (b) hepatic total cholesterol, (c) plasma triglycerides and (d) hepatic triglycerides levels in BALB/c mice. **Statistically significant (P<0.05), ns, not statistically significant*.

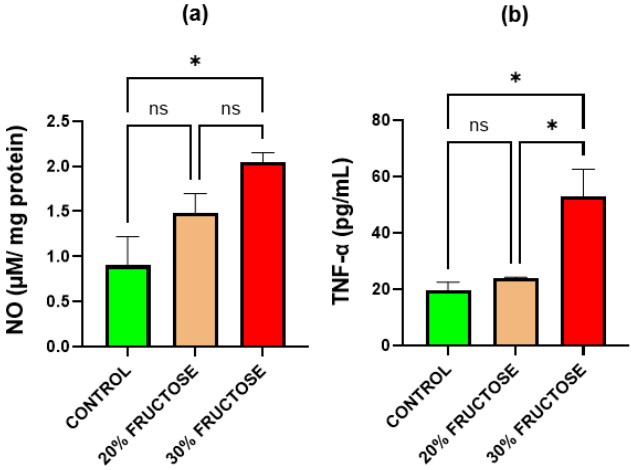

Figure 4: Effect of fructose consumption on hepatic concentrations of (a) nitric oxide and (b) tumour necrosis factor alpha in BALB/c mice. **Statistically significant (P<0.05), ns, not statistically significant*.

3.4. Effect of fructose on oxidative stress indices

Figure 5 shows the responses of oxidative stress markers to fructose feeding in mice. There is a decrease in hepatic levels of GSH in the fructose-administered mice relative to controls (Figure 5b). However, the observed decrease in hepatic GSH levels was not statistically significant in both the 20% and 30% fructose groups. The activity of SOD decreased in response to fructose feeding, although when compared with the control, the decrease was statistically significant in only the 30% fructose group (Figure 5b). Similarly, the activities of CAT and GSH-Px were significantly reduced only in the 30% fructose group compared with the control (Figure 5c and 5d). As shown in Figure 5(e), the concentration of the lipid peroxidation product, MDA, increased significantly in response to fructose feeding.

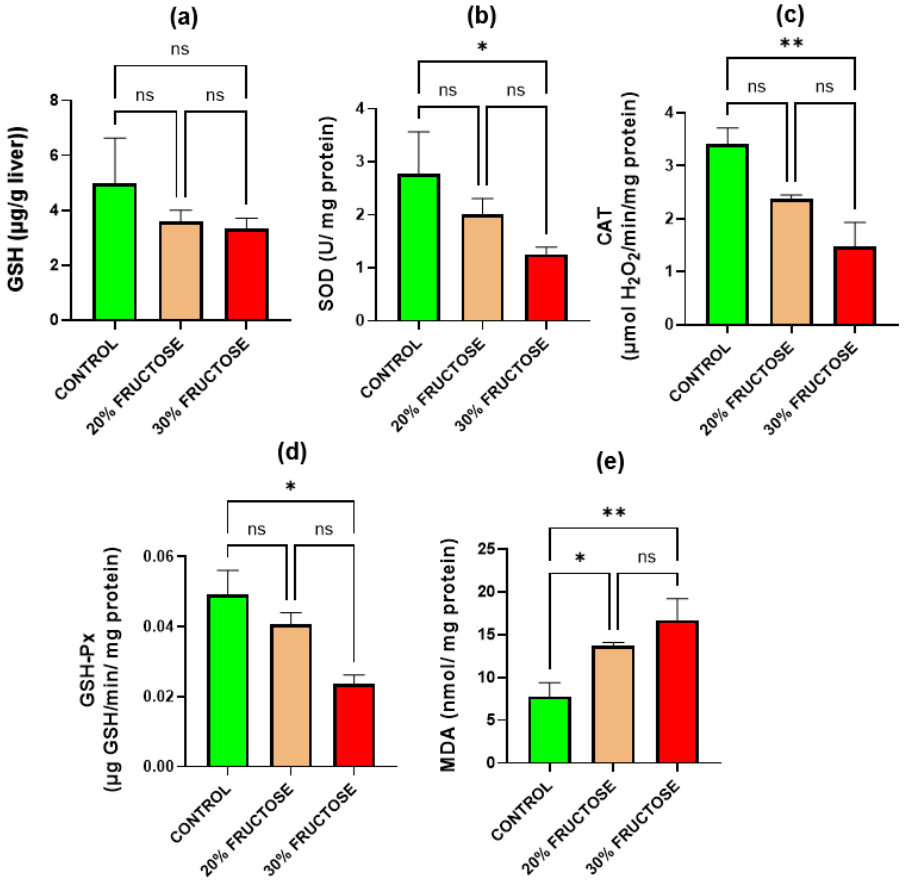

Figure 5: Effect of fructose consumption on hepatic (a) reduced glutathione level, (b) superoxide dismutase activity, (c) catalase activity, (d) glutathione peroxidase activity, and (e) malondialdehyde level in BALB/c mice. **Statistically significant (P<0.05), ns, not statistically significant*.

3.5. Effect of fructose on liver function biomarkers

As shown in Figure 6a, the plasma level of ALT increased significantly *(P < 0.05)* in the fructose-fed mice compared with the control. Similarly, plasma AST levels significantly increased in the 20% and 30% fructose groups compared with the control group.

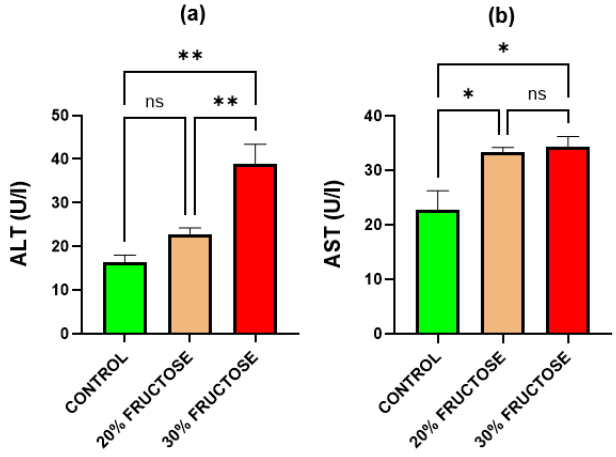

Figure 6: Effect of fructose consumption on plasma activities of (a) alanine aminotransferase, and (b) aspartate aminotransferase in BALB/c mice. **Statistically significant (P<0.05), ns, not statistically significant*.

3.6. Effect of fructose on liver histoarchitecture

Figure 7 shows the representative images (x400) of hematoxylin and eosin-stained formalin-fixed paraffin-embedded liver sections of control mice and fructose – treated mice. In the control (Figure 7a), the hepatic lobules maintain normal organisation; portal tracts and central veins appear normal. Hepatocytes exhibit uniform cytoplasmic density. Sinusoidal endothelial cells and Kupffer cells show no reactive changes, and there is an absence of focal inflammation or cellular degeneration.

In the liver section from the 20% fructose-treated mice (Figure 7b), portal tracts are minimally expanded without disrupting architecture. Hepatocytes irregularly contain small, clear cytoplasmic vacuoles; however, nuclei remain centrally located, and there is mild lobular inflammation. Kupffer cell numbers are mildly increased, and morphology is unchanged.

In the liver section from the 30% fructose-treated mice (Figure 7c), lobular architecture shows moderate centrilobular congestion and mild distortion. Portal regions contain small aggregates of mononuclear inflammatory cells. About 15–20% of hepatocytes demonstrate microvesicular steatosis, with scattered apoptotic bodies, and Kupffer cell hyperplasia.

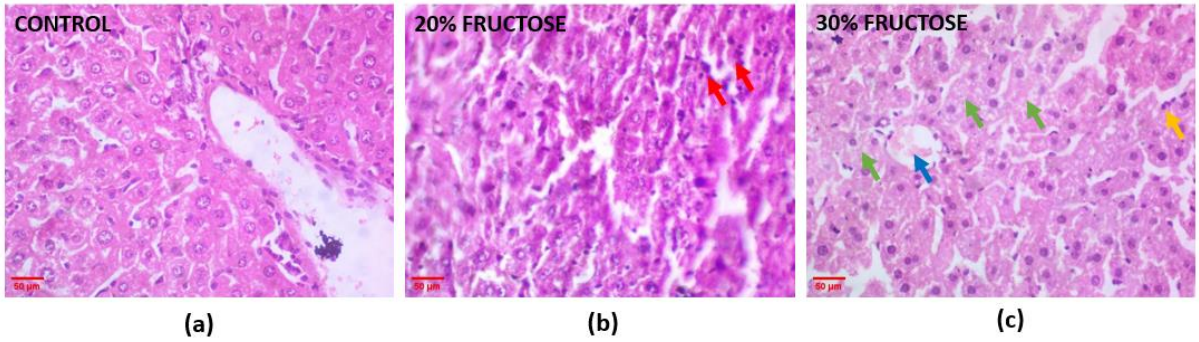

Figure 7: Representative images (x400) of liver sections showing the effect of fructose administration in albino mice (BALB/c mice): (a) control, (b) 20% Fructose and (c) 30% Fructose.

4. Discussion

The current study evaluated the effect of short-term fructose intake in a dose-dependent manner in BALB/c mice. Data obtained indicated metabolic alterations, inflammatory response, and alterations in liver architecture, with stronger effects observed at 30% fructose intake. Findings from the present study align with the growing body of evidence from other experimental models implicating excessive fructose intake as a key driver of insulin resistance, dyslipidaemia, oxidative stress, and early-stage metabolic dysfunction–associated steatotic liver disease (Hannou et al., 2018).

The observed increases in plasma glucose and insulin concentrations, as well as a higher insulin resistance index, indicate the onset of insulin resistance following fructose intake (Softic et al., 2020). These findings are supported by the previously published literature, which demonstrated that metabolism of fructose leads to enhanced hepatic glucose output and reduced insulin action (Elliott et al., 2002; Özer et al., 2025). It was also demonstrated earlier that chronic fructose feeding led to insulin resistance accompanied by de novo lipogenesis and lipid accumulation in the liver (Softic et al., 2020).

The significant increase in body weight occurred only in the 30% fructose group, demonstrating the dependency of the effect on the dose. Several other studies have obtained comparable results reporting that high concentrations of fructose or prolonged duration of administration lead to body weight alteration (Elliott et al, 2002; Mamikutty et al., 2014). The lack of significant weight gain in the 20% fructose-treated group, despite metabolic perturbations, may be attributed to the fact that metabolic dysregulation often precedes the onset of obesity.

Additionally, fructose intake for twenty-one days caused significant increases in plasma and hepatic triglycerides and total cholesterol concentration, especially in 30% group. These findings are supported by previous research indicating that fructose enhances de novo synthesis of lipids in the liver (Stanhope et al., 2009; Chong et al., 2019). Although the triglyceride level was increased in both groups receiving fructose, the statistically significant alterations of lipids were seen only at 30% dosage. This finding is consistent with that demonstrated by Spruss et al. (2009), who reported high hepatic lipid accumulation in 30% fructose feeding in C3H/HouJ and C3H/HeJ mice. The lipid alterations observed in this study are central to the pathogenesis of MASLD and reinforce the lipogenic role of fructose in the disease.

An increase in NO and TNF-α in the 30% fructose-fed group indicates the induction of inflammatory processes. TNF-α is one of the key proinflammatory cytokines involved in the development of insulin resistance and inflammation during fructose administration, as reported previously (Kanuri et al., 2011; Vachliotis & Polyzos 2023). An elevation in the NO levels in the fructose groups indicated the induction of iNOS in response to metabolic and oxidative changes in the liver (Jegatheesan & De Bandt, 2017).

Administration of fructose resulted in decreased activity of antioxidant enzymes – SOD, CAT, and GSH-Px, as well as an increase in MDA level. These findings agree with previous data on ROS accumulation as a consequence of fructose consumption, leading to the depletion of antioxidant capacity (Mazzoli et al., 2021; Midorikawa et al., 2024). The decrease in GSH level could serve as evidence for early oxidative impairment. However, the non-statistically significant decrease in GSH content between the two fructose groups may indicate initial stages of depletion or compensatory mechanisms. Statistically significant decreases in antioxidant enzyme activities were observed only in the 30% group, indicating a dose-dependent pattern of fructose-induced oxidative stress. The observed increase in MDA levels further confirms enhanced lipid peroxidation, a hallmark of oxidative damage in hepatic tissues in MASLD (Ore & Akinloye, 2019).

Elevation in the levels of both ALT and AST in the plasma of fructose-fed animals suggests hepatocellular injury with loss of cell membrane integrity. These biomarkers have been used in previous studies to confirm fructose-induced hepatotoxicity and liver damage (Abdelmalek et al., 2010; Lim et al., 2010). Histological evaluation revealed progressive liver damage due to fructose intake, with mild microvesicular steatosis, minimal inflammation in 20% fructose group, and architectural distortion, centrilobular congestion, inflammatory cell infiltration, and a higher level of steatosis in 30% group. These findings are consistent with a previous report on fructose-induced steatosis and hepatocellular injury in MASLD (Kanuri et al., 2011).

5. Conclusion

Fructose administration via drinking water induces dose-dependent metabolic and hepatic alterations in BALB/c mice. The low dose of fructose (20%) induced mild alterations in both biochemical and histological indicators. In comparison, the higher dose (30%) caused significant metabolic disruption, oxidative damage, inflammation, and liver injury, indicating the involvement of excessive fructose intake as an essential risk factor for the development of IR and MASLD in BALB/c mice.

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