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METABOLIC ENDOTOXEMIA: ANTIOXIDANT POTENTIAL OF ASCORBIC ACID

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Abstract
There is a global increase in fructose intake through the consumption of sweetened beverages. High fructose consumption has been linked with oxidative and metabolic disturbances. Ascorbic acid (commonly known as Vitamin C) is a potent antioxidant that positively boosts the oxidative and metabolic systems. This study aimed to investigate the impact of vitamin C supplementation on serum and kidney oxidative stress markers in male Wistar rats fed with high fructose drink.
Twenty (20) adult male Wistar rats (120±20g) were acclimatized for 14 days and randomly assigned into four groups with five rats per group (n=5) were used for this study. Group 1 (Control group) received normal rat feed and distilled water; Group 2 (Vit C) received normal rat feed and 100ml of distilled water with 1g of vitamin C; Group 3 (HFD) was given normal rat feed and 100ml of distilled water with 30g of fructose; and Group 4 (HFD+Vit C) received 100ml of distilled water with 1g of vitamin C and 30g of fructose. At the end of 4 weeks, the animals were sacrificed following standard laboratory procedures. Serum was obtained from the blood samples, and the kidneys were harvested, homogenized, and decanted for the analysis of malondialdehyde (MDA), Superoxide Dismutase (SOD), Glutathione (GSH), and catalase (CAT) levels in the serum and kidney tissues. Statistical analysis was conducted using one-way ANOVA in Graph Pad Prism 8.0, with a significance level of $p \leq 0.05$.
Results showed that the high fructose fed group exhibited a significant increase ($p \leq 0.05$) in MDA levels (12.74±0.91) compared with the control group (8.53±0.31) and reduced SOD levels (0.60±0.02) compared with the control group (1.54±0.06). There was also a significant decrease ($p \leq 0.05$) in GSH levels (11.66±0.43) compared with the control group (21.83±0.27) and reduced CAT activity (1.60±0.19) compared with the control group (5.60±0.36), indicating increased lipid peroxidation and impaired antioxidant defenses.
Vitamin C supplementation effectively reduced MDA levels while restoring SOD, CAT, and GSH activity, indicating its protective role in mitigating fructose-induced oxidative stress. These findings highlight vitamin C's potential as an antioxidant intervention to counteract oxidative damage and renal dysfunction caused by high fructose consumption.

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Introduction

Fructose consumption has increased significantly worldwide, especially through sweetened beverages. Research shows that high fructose intake can lead to several metabolic abnormalities, such as insulin resistance, hyperuricemia, dyslipidemia, and obesity [1]. Fructose metabolism, primarily in the liver, produces excessive ROS, leading to oxidative stress and inflammation, which can extend to other organs, including the kidneys [2]. Several studies have indicated that chronic intake of high-fructose diets leads to renal oxidative stress and impairs kidney function [3]. In experimental models using male rats, the administration of a high-fructose diet has been shown to induce oxidative stress, promoting the generation of lipid peroxidation products such as malondialdehyde (MDA) and reducing the levels of endogenous antioxidants like superoxide dismutase (SOD) and catalase (CAT) [4]. This indicates that prolonged high fructose consumption can overwhelm the kidney's antioxidant defenses, causing renal damage.

Vitamin C, also known as ascorbic acid, is a potent antioxidant known for its ability to neutralize free radicals, regenerate other antioxidants such as vitamin E, and support overall cellular health [5]. It plays a critical role in reducing oxidative stress by scavenging ROS and upregulating the activity of enzymatic antioxidants, such as glutathione peroxidase and catalase [6]. Vitamin C supplementation has been shown to mitigate oxidative stress-induced damage in various animal models, particularly in conditions involving high fructose intake [7]. The administration of vitamin C in rats subjected to high-fructose diets reduced the serum and tissue levels of oxidative stress markers, such as MDA, while increasing the activity of endogenous antioxidants [8]. This indicates that vitamin C could serve as a protective agent against fructose-induced oxidative damage in the kidneys.

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses. Excessive ROS can cause damage to lipids, proteins, and DNA, leading to various chronic diseases, including renal dysfunction [9]. As major organs involved in filtering blood and regulating bodily fluids, the kidneys are particularly susceptible to oxidative damage due to their high metabolic activity and exposure to various toxins and metabolic waste products [10]. Oxidative stress markers, such as MDA, are widely used to assess lipid peroxidation, whereas SOD and CAT are used to evaluate antioxidant enzyme activities. Measuring these markers in both serum and kidney tissue provides a comprehensive assessment of systemic and localized oxidative stress levels [11].

Given the rising global consumption of fructose-rich diets and the associated increase in metabolic disorders, understanding the impact of fructose on renal health is crucial. Although fructose-induced oxidative stress has been extensively studied, the potential protective role of antioxidants like vitamin C, in mitigating renal damage remains an area of interest.

Materials and Methods

Experimental design

Twenty adult male Wistar rats of comparable weights (120±20g) were used in this study. The rats were obtained from the animal house, Department of Physiology, College of Medicine, Ambrose Alli University, Ekpoma, and transferred to the Department of Physiology animal holding facility in the same institution. They were housed in a plastic cage with a wire screen top. The animals were fed with drinking water and pelleted rat feed during acclimatization (14 days) and were maintained under standard care of laboratory animals as stated in the guidelines and regulations for the use of animals in scientific experiments.

Preparation and administration of substances

Vitamin C tablets and Fructose were obtained from a standard pharmacy in Ekpoma, Edo state. The Vitamin C tablets were crushed into powder using a laboratory mortar and pestle. The high-fructose drink was prepared by dissolving 30g of fructose in 100ml of distilled water, the vitamin C drink was prepared by dissolving 1g of vitamin C in 100ml of distilled water, and the high-fructose and vitamin C drink mixture was prepared by adding 30g of fructose and 1g of vitamin C to 100ml of distilled water. The correct quantities of fructose and vitamin C were measured using an electronic sensitive scale, distilled water was measured using a measuring beaker, and different water compositions were prepared daily for the duration of the experiment.

Experimental grouping

After acclimatization, the rats were assigned to four (4) groups of five (5) rats each as follows:

Group 1(Control group) was given normal rat feed and 100ml of distilled water. Group 2 (Vit C): rats were given normal rat feed and 100ml of distilled water with 1g of vitamin C. Group 3 (HFD): rats were given normal rat feed and 100ml of distilled water with 30g of fructose. Group 4 (HFD+Vit C): rats were given normal rat feed and 100ml of distilled water with 1g of vitamin C and 30g of fructose. The administration lasted for 28 days.

Sample collection

At the end of the experiment, blood samples were obtained following standard laboratory procedures by cardiac puncture with a needle and syringe and collected into EDTA bottles for analysis. Kidneys were also harvested.

Sample analysis

The blood in EDTA bottles were centrifuge at 3000 rpm for 10 minutes to obtain the serum while the kidneys were harvested, homogenized and decanted for analysis. Serum and kidney tissue concentrations of malondialdehyde (MDA), Superoxide Dismutase (SOD), Glutathione (GSH), and catalase (CAT) were then determined using a UV spectrophotometer.

Statistical analysis

Data were analyzed with GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA) and expressed as the means SE. One-way ANOVA was used for comparisons, followed by post hoc Newman-Keuls Multiple Comparison test. Results were statistically significant at $P \leq 0.05$.

Results

Malondialdehyde (MDA) levels (uM/L)

Figure 1 shows the effect of high-fructose drink and vitamin C on malondialdehyde (MDA) levels in serum and kidney tissue in male Wistar rats.

Serum MDA levels elevated significantly ($p \leq 0.05$) in HFD (12.74±0.91) compared to the control group (8.22±0.20) and HFD+ Vit C group.

Kidney tissue MDA levels was raised significantly ($p \leq 0.05$) in HFD (13.23±0.37) and HFD+ Vit C (10.10±0.042) groups compared with the control group (8.53±0.31) and HFD+ Vit C groups.

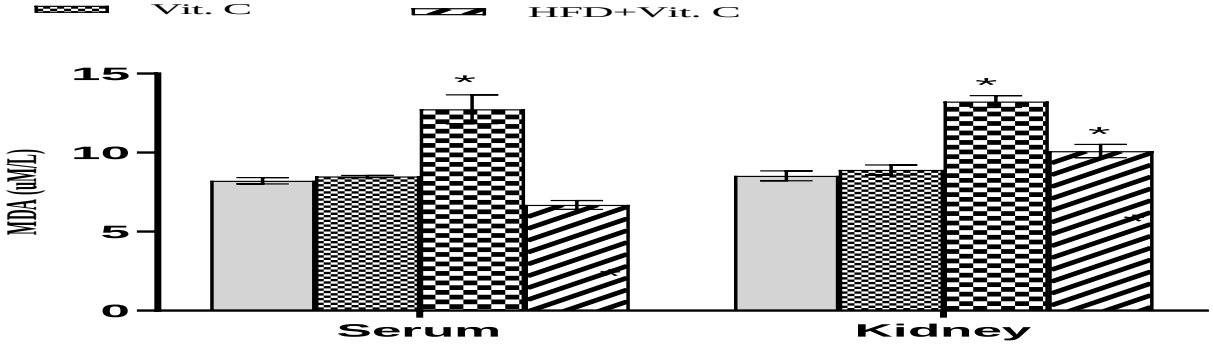

Figure 1 MDA levels in serum and kidney tissue

The results are presented as mean ± SEM, n=5, * vs CN

CN= Control group, HFD= High fructose drink; Vit, C= Vitamin C, HFD+Vit. C= High fructose drink and Vitamin C, MDA= Malondialdehyde

Superoxide Dismutase (SOD) activity (U/mg)

Figure 2 shows the effect of high fructose drink and vitamin C on superoxide dismutase (SOD) activity in the serum and kidney tissue of male Wistar rats.

Serum SOD activity decreased significantly ($p \leq 0.05$) in the HFD group (0.60±0.02) compared to the control group (1.54±0.06) and HFD+ Vit C group.

Kidney tissue SOD activity decreased significantly in the HFD group (0.66±0.03) compared to the control group (1.89±0.12) and HFD+ Vit C group.

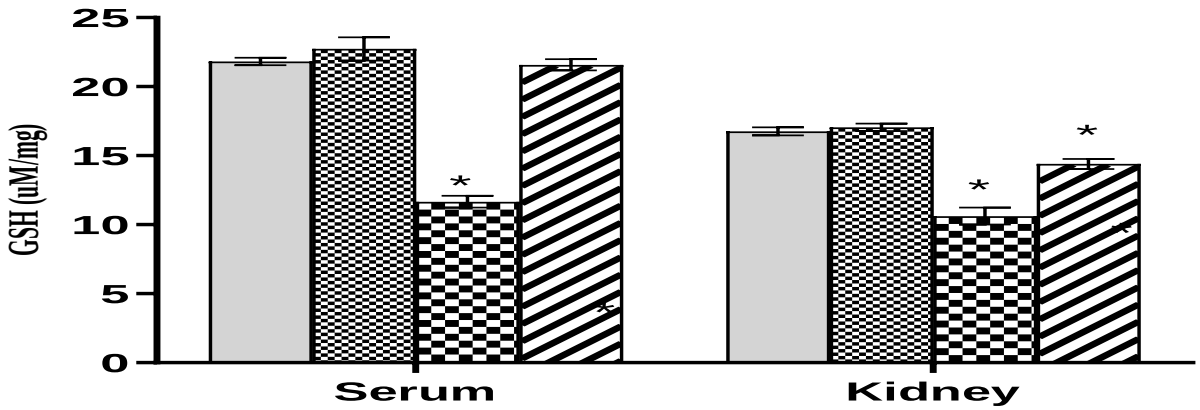

Figure 2 SOD activity in serum and kidney tissue

The results are presented as mean ± SEM, n=5, *vs CN

CN= Control group, HFD= High fructose drink; Vit, C= Vitamin C, HFD+Vit. C= High fructose drink and Vitamin C, SOD= Superoxide dismutase

Glutathione (GSH) levels (uM/mg)

Figure 3 shows the effect of high fructose drink and vitamin c on Glutathione (GSH) levels in serum and kidney tissue in male Wistar rats.

Serum GSH levels were significantly reduced in the HFD group (11.66±0.43) compared to the control group (21.83±0.27) and HFD+ Vit C group.

Kidney tissue GSH levels decreased notably in HFD (10.62±0.62) and HFD+Vit C group (14.40±0.37) compared to the control group (16.76±0.30).

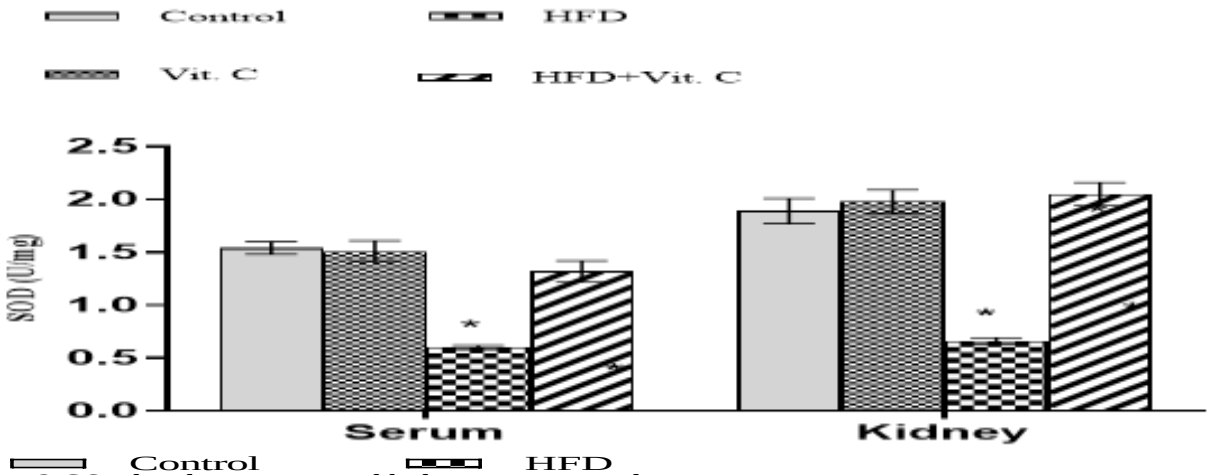

Figure 3 GSH levels in serum and kidney tissue samples

The results are presented as mean ± SEM, n=5, * vs CN

CN= Control group, HFD= High fructose drink; Vit, C= Vitamin C, HFD+Vit. C= High fructose drink and Vitamin C, GSH= Glutathione

Catalase (CAT) activity (U/mg)

Figure 4 shows the effect of high fructose drink and vitamin c on Catalase (CAT) activity in serum and kidney tissue of male Wist

Serum CAT activi gnificant e HFD g 9) comp the control group (5.60±0.36) and HF

Kidney tissue CAT ed notab e HFD the control group (5.54±0.46) and HF

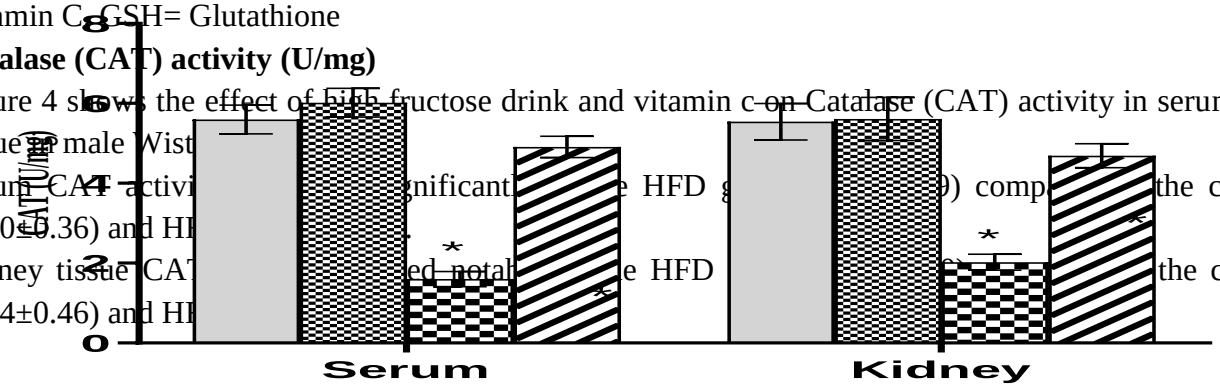

Figure 4 CAT activity in the serum and kidney

The results are presented as mean ± SEM, n=5, * vs CN

CN= Control group, HFD= High fructose drink; Vit, C= Vitamin C, HFD+Vit. C= High fructose drink and Vitamin C, CAT= Catalase

Discussion

Increased consumption of fructose has been linked with metabolic disorders and endotoxemia. A disruption in the activities of antioxidants in living systems is a risk factor for endotoxemia development. Results from this study show a significant increase in serum and kidney MDA levels in the HFD group when compared to the control group and the HFD+Vit.C supplemented groups. [14] opined that Wistar rats on a high fructose diet exhibited elevated malondialdehyde (MDA) levels due to increased lipid peroxidation caused by reactive oxygen species (ROS) overload. Fructose metabolism in the liver generates excess ROS, which attack membrane lipids, forming MDA as a byproduct of oxidative damage. This oxidative stress leads to the depletion of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), weakening the body's defense against ROS. In addition, studies by [12] and [13] stated that Wistar rats on a high fructose diet exhibited elevated malondialdehyde (MDA) levels in serum due to increased lipid peroxidation and oxidative stress caused by excessive reactive oxygen species (ROS) generation during fructose metabolism. However, vitamin C supplementation in the HFD+Vit C group counteracted these effects in the serum. This finding was in line with the work of [14], who reported that Vitamin C can scavenge free radicals, reduce lipid peroxidation, and restore antioxidant enzyme activity. As a potent water-soluble antioxidant, vitamin C donates electrons to neutralize ROS before they initiate oxidative damage, thereby lowering MDA levels and enhancing SOD, CAT, and GSH activity, ultimately protecting the kidney and serum antioxidant balance from fructose-induced oxidative stress. However, in the kidney, the MDA levels in HFD+Vit. C group as reported in the studies, a slight increase was observed, though significant. This increase could be linked to the acute nature of the studies as well as the metabolic roles of the kidney. Hence, vitamin C supplementation could suppress MDA expression in the serum but not in the kidney tissue.

Serum and kidney tissue SOD levels in this study showed a significant decrease in the HFD group compared with the control group and the VIT.C supplemented groups. This is in agreement with the findings of [15]; [16] and [14], who stated that Wistar rats on a high-fructose diet exhibited reduced superoxide dismutase (SOD) levels due to excessive reactive oxygen species (ROS) production and oxidative stress caused by fructose metabolism. High fructose intake leads to mitochondrial dysfunction, increased uric acid levels, and NADPH oxidase activation, all of which contribute to ROS accumulation. This oxidative overload depletes SOD activity, impairing the enzyme's ability to convert superoxide radicals (O_2^-) into hydrogen peroxide (H_2O_2), further worsening cellular damage [2]. Vitamin C supplementation as observed in this study, most probably counteracted this by acting as a strong antioxidant, scavenging ROS, preventing further SOD depletion, and restoring its enzymatic activity. Vitamin C stabilizes superoxide radicals, reduces oxidative burden, and enhances the regeneration of antioxidant enzymes, ultimately protecting serum and kidney tissues from oxidative stress and improving overall redox balance. As a redox agent, vitamin C donates electrons to neutralize ROS, restores SOD levels by reducing oxidative stress, and improves antioxidant enzyme efficiency, ultimately protecting serum and kidney tissues from oxidative damage and restoring redox homeostasis [15].

A significant decrease in serum and kidney tissue GSH levels was observed in the HFD group compared with the control group and Vit. C-supplemented groups were reported in this study. A study by [17] showed that Wistar rats on a high-fructose diet exhibited depletion of glutathione (GSH) levels due to excessive reactive oxygen species (ROS) production and oxidative stress resulting from fructose metabolism. High fructose intake led to mitochondrial dysfunction, increased uric acid production, and NADPH oxidase activation, which significantly elevated superoxide radicals (O_2^-) and hydrogen peroxide (H_2O_2). This oxidative overload caused GSH depletion because GSH is a crucial antioxidant responsible for neutralizing ROS and maintaining cellular redox balance. The reduction in GSH weakened the cellular antioxidant defense system, increasing susceptibility to lipid

peroxidation, protein oxidation, and renal dysfunction. [8] Also noted that high fructose intake leads to oxidative imbalance, which depletes GSH stores, as GSH is required to neutralize ROS and protect cellular components from oxidative damage. Reduced GSH levels impair the cell's ability to detoxify ROS, further worsening oxidative stress in serum and kidney tissue. Significant increase as reported in the Serum of the Vit. C supplemented group indicates that Vitamin C supplementation might act as a potent antioxidant, scavenging ROS, regenerating GSH levels, and enhancing the activity of antioxidant enzymes. Vitamin C is a redox-active molecule that converts oxidized glutathione (GSSG) back into its reduced form (GSH), restoring antioxidant defenses, maintaining redox homeostasis, and protecting kidney and serum tissues from oxidative stress-induced damage [14]. Again, this significant increase was not yet actuated in the Vit-derived kidney tissue. C-supplemented group as reported for MDA expression.

Serum and kidney tissue CAT levels show a significant decrease in the HFD group when compared to the control group and the Vit.C-supplemented groups. [13] and [3] reported that Wistar rats on a high-fructose diet exhibited reduced catalase (CAT) levels due to excessive reactive oxygen species (ROS) generation and oxidative stress. The suspected mechanism underlying this altered CAT levels is the same as the mechanism responsible for altered SOD and GSH levels as reported earlier. [15]; [4] opined that under normal conditions, CAT is responsible for breaking down H_2O_2 into water and oxygen, preventing oxidative damage. However, prolonged exposure to oxidative stress from fructose metabolism depleted CAT levels, impairing the cell's ability to detoxify H_2O_2, which further intensified lipid peroxidation, inflammation, and kidney dysfunction. Vitamin C supplementation mitigated this effect by acting as a potent antioxidant, neutralizing ROS, preventing CAT depletion, and enhancing its enzymatic activity. As a redox-active compound, vitamin C protects CAT from oxidative degradation, stabilizes free radicals, and supports the regeneration of antioxidant enzymes, ultimately restoring CAT function and reducing oxidative stress in serum and kidney tissues [15].

In conclusion, the assayed markers of oxidative disturbance showed a significant increase in MDA, as well as a significant decrease in SOD, GSH, and CAT in the serum and kidney tissue of HFD patients. High fructose solution intake most probably could lead to oxidative disturbance in the blood and kidney. The intervention of vitamin C supplementation implies that vitamin C might can block reactive oxygen species due to its free scavenging properties and maintain membrane integrity. Hence, Vitamin C could be used as a potent antioxidant to alleviate oxidative stress.

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