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Effect of Vitamin D_3 (Cholecalciferol) on Cardiac Redox Homoeostasis in Male Wistar Rats Fed High Sucrose Diet

Adenike Endurance Omotehinse[1*], Adewumi Oluwafemi Oyabambi[1], Josephine Utibe Okonko[2], Blessing Francis[2], Victory Fegor Ojeje[3]

[1]Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Ilorin, Kwara State, Nigeria
[2]Department of Human Physiology, Faculty of Basic Medicine Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Amassoma, Bayelsa State, Nigeria
[3]Department of Pharmaceutics and Industrial Pharmacy, Delta State University Abraka, Delta State, Nigeria

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***Corresponding author:** Adenike Endurance Omotehinse
Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Ilorin, Kwara State, Nigeria

Abstract **Original Research Article**

An imbalance in redox environment can lead to oxidative stress, which has emerged as a growing health concern as it constitutes one of the significant risk factors of cardiovascular diseases. Vitamin D3, in addition to its classical role in calcium homeostasis, exerts various biological actions that are beneficial in the management of inflammatory disorders such as cardiovascular disease, diabetes, and hypertension. An animal study suggests that Sucrose, a non-reducing disaccharide composed of glucose and fructose subunits, can promote metabolic disturbances and contribute to oxidative stress when consumed in excess. This research aims to examine the effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed a high-sucrose diet. Twenty-four (24) male Wistar Rats weighing 150-200g were divided into four (4) groups of six rats as: Control (Ctr: normal chow + vehicle: normal saline), Sucrose (40g dissolved in 100ml of distilled water), Vitamin D3 (1500IU/kg dissolved in 3ml of olive oil) orally, and 40% Sucrose solution + Vitamin D3 (1500IU/kg). After six weeks, animals were anesthetized with 50mg/kg Ketamine hydrochloride administered intramuscularly, and blood was collected via cardiac puncture. Plasma and cardiac homogenate were analyzed, and data were expressed as mean ± SEM; $p < 0.05$ was considered statistically significant. Sucrose significantly reduced plasma and cardiac NADPH, G6PDH, and GSH compared to control. Sucrose also reduced plasma GPX, but did not exhibit significant effect on cardiac GPX compared to control. Vitamin D3 on the other hand caused a substantial increase in plasma and cardiac NADPH, G6PDH, GSH, and GPX compared to control. This study conclusively shows that administration of vitamin D3 ameliorated oxidative stress induced by a high sucrose diet and, as such, has cardioprotective effects.

Keywords: Vitamin D3, Cholecalciferol, Sucrose, Cardiac redox homeostasis, Oxidative stress, Plasma and Cardiac makers of oxidative stress.

1. INTRODUCTION

Redox homeostasis is essential for the maintenance of many cellular processes including responses to reactive oxygen species, signaling, protection of protein thiols, oxidation- reduction reactions as well as the removal of xenobiotics. The redox environment of a cell compartment is the overall balance of its oxidation/reduction systems (Schsaffer & Buettner, 2001). An imbalance in this redox environment can lead to oxidative stress.

Oxidative stress leads to a number of diseases, from neurodegenerative disease to cardiovascular diseases and type 2 diabetes (Wright *et al*., 2006). Cardiovascular disease (CVD) is still the leading cause of death worldwide, accounting for almost 18 million victims in 2019 (WHO, 2022). The social and economic cost of cardiovascular disease is constantly rising due to the increase of elderly population, the spread of metabolic disorders and known risk factors for cardiovascular disease. CVD comprises condition that affect the heart or blood vessels such as coronary heart disease, stroke, peripheral arterial disease, congestive

heart failure, heart arrhythmia, congenital heart disease, endocarditis and aortic disease (WHO, 2022).

Oxidative stress originates in cells and tissues when reactive oxygen species (ROS) accumulate, due to an imbalance between ROS production and antioxidant defenses. ROS are unstable molecules comprising of oxygen free radicals (superoxide, hydroxyl radicals, and peroxyl radicals), and non-radicals (hydrogen peroxide, and hypochlorous acid) (Liochev, 2013). ROS are produced mainly by mitochondria along the respiratory chain, but other organelles, such as the peroxisome and endoplasmic reticulum may contribute to ROS formation, besides endogenous processes, ROS levels can be increased by exogenous sources including pollutants, radiations, cigarette smoking, xenobiotics, certain foods and drugs (Bhattacharyya *et al*., 2014).

Sucrose, a non- reducing disaccharide sugar, composed of glucose and fructose subunits has been implicated in promoting metabolic disturbances and contributing to oxidative stress when consumed in excess quantity (Shaw *et al*., 2010). A high sucrose diet may result in hyperglycemia, which is associated with the formation of glycated products (Garaschuk *et al*., 2018). These events trigger free radical overproduction and antioxidant defense impairment, leading to cell damage and disease progression (Forbes *et al*., 2008; Luschak *et al*., 2011). Consequently, a high sucrose diet can induce reactive oxygen species production, indirectly through modified biomolecules (Semchyshyn *et al*., 2011). To counteract the production of ROS, numerous endogenous and exogenous antioxidant factors are present within the cells. Among endogenous antioxidants there are enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), peroxiredoxin (Prx), and compounds, particularly reduced glutathione (GSH). Exogenous antioxidants comprise mainly vitamins and pro- vitamins.

Vitamin D3 is a fat soluble seco-steroid produced from cholesterol. Although vitamin D3 is classically well known for its role in growth and remodeling of bone, it also plays vital role in calcium/phosphorus homeostasis. Recent studies have identified a much broader spectrum of its activities. It is now well recognized as an important hormone playing a role in human homeostasis (Walentowicz-Sadlecka *et al*., 2013). In 1993, wiseman first demonstrated that vitamin D3 is a potent antioxidant vitamin, preventing iron dependent lipid peroxidation in the cell membrane and acting similar to the anti-cancer drug; tamoxifen (Wiseman, 1993). Since then, many studies have been conducted to better identify the therapeutic antioxidant roles of vitamin D3 (Ke *et al*., 2016).

Vitamin D3 has the capacity to reduce oxidative stress through the positive regulation of cellular glutathione (GSH) and superoxide dismutase (SOD). Vitamin D3 and its metabolite can inhibit nuclear transcription factor kappa (kB) by increasing IkB expression and reducing IkB alpha phosphorylation. Therefore, vitamin D3 decreases the generation of free radicals and inflammatory cytokines, mainly by deactivating NF-kB-dependent pathways, showing its favorable effects on oxidative stress reduction (Sepidarkish *et al*., 2019). In animal studies, high Sucrose diet has been implicated in the etiology of many diseases with pronounced effects on various organs, such as liver, kidney, and brain to mention but few (Busserolles *et al*., 2002). However, studies systemically exploring the impact of sucrose on redox homeostasis in the heart appears sparse in data.

Vitamin D3, a fat soluble seco-steroid classically well known for its role in growth and remodeling of bone, as well as calcium/phosphorus homeostasis, has recently been identified as an important hormone playing a role in human homeostasis (Walentowicz-Sadlecka *et al*., 2013). To date, evidence regarding the effect of vitamin D3 in redox homeostasis imbalance linked with high sucrose diet is lacking. Therefore, this study intends to address the paucity of available data and find the effect vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet. Results from this study shows that Vitamin D3 has a cardioprotective effects by ameliorating oxidative stress resulting from an imbalanced redox homeostasis caused by high sucrose diet by increasing plasma and cardiac NADPH, G6PDH, GSH, and GPX.

2. MATERIALS AND METHODS

2.1 Materials

The following materials were utilized in the course of this study:

- Experimental Animals: Twenty-four (24) male Wistar rats.
- Housing: Wired gauze cages equipped with feeding bowls and water bottles.
- Bedding: Standard wood shavings.
- Diet: Commercial rats' pellet and tap water were provided *ad libitum*.
- Weighing and Measurement: A sensitive weighing scale and a measuring cylinder.
- Administration and Sampling: 2ml and 5ml syringes, an oral cannula, heparinized bottles, and plain bottles.
- Dissection and Preparation: A standard dissecting set, razor blades, a beaker, and cotton wool.
- Anesthesia: Ketamine hydrochloride.
- Laboratory Supplies: Disposable latex gloves, phosphate-buffered saline (PBS), office pins, permanent markers, liquid soap, and methylated spirit.

2.2 Chemicals and Drugs

The following chemicals and pharmacological agents were utilized in the study:

- Induction Agent: Vitamin D3 (Cholecalciferol).
- Vehicle/Solvent: Olive oil, distilled water, and normal saline (0.9% NaCl).
- Dietary Component: Sucrose.

Vitamin D3 was purchased from Rota medics Pharmacy, Ilorin, Kwara State. Sucrose was purchased from Brig biotech, Ilorin Kwara State. The chemicals were of analytical grade.

2.2 METHODOLOGY

2.2.1 Experimental Animals and Care

Twenty-four (24) adult male Wistar rats weighing 150g - 200g were used for the study. The animals were obtained from trusted animal breeder in Ibadan metropolis. Rats were housed in plastic cages at a room temperature and a photoperiodicity of 30 degrees in 12hours light/12 hours dark respectively, at the University of Ilorin Teaching Hospital Animal House with free access to food and water *ad libitum*. The standard laboratory diet was purchased from Chikun feed industries at Ilorin, Nigeria. All animals were housed under the same environmental conditions for a week before experimentation for acclimatization and to ensure normal growth and behavior. After the week of acclimatization, the rats were randomly allotted to separate groups. The management of the rats was in compliance to the National Academy of Sciences report (National Academy of Science, 2011) and the requirements of the Ethical Board of the University of Ilorin, Ilorin, Nigeria.

2.2.2 Experimental Procedure

The experiment was performed in accordance with the National Institute of Health (NIH) guidelines for the care and use of laboratory animals and approval was gotten from the ethical review committee of the College of health sciences, University of Ilorin, Nigeria. The rats were acclimatized for two weeks after which administration began. The administration lasted for six weeks

2.2.3 Experimental Design

Twenty-four (24) Wistar Rats were divided into four (4) groups consisting of six (6) rats per cage. n=6.
Rats in group A (Control group) were given 0.5ml of normal saline.
Rats in group B were given daily dose of 40% sucrose solution ad libitum.
Rats in group C were given daily dose of Vitamin D3 (1500IU/kg) dissolved in 3ml of olive oil orally using oral cannula.
Rats in group D were given daily dose of 40% Sucrose solution ad libitum and Vitamin D3 (1500IU/kg) dissolved in 3ml of olive oil orally using oral cannula**.**

Table 1: Groupings Of Experimental Animals

GROUPS	CONTENT
A	Control
B	Sucrose
C	Vitamin D_3
D	Sucrose + Vitamin D_3

2.2.4 Body Weight Measurement

The body weights of all experimental animals were monitored longitudinally as a primary indicator of physiological status. Measurements were taken once per week using a sensitive electronic weighing balance. Each rat was gently placed in a clean, tared container on the balance, and the weight was recorded in grams (g) to the nearest 0.1 g.

2.2.5 Food Intake Measurement

Daily food consumption was quantified to assess metabolic and nutritional changes. A pre-weighed amount of standard rat pellet was provided to each cage at the same time daily. After 24 hours, the remaining food, including any spillage collected from the cage bottom was carefully weighed. The daily food intake (in grams) for each group was calculated using the formula: Food Intake (g) = [Initial Food Weight (g)] – [Weight of Leftover Food (g)].

2.2.6 Water Intake Measurement

Daily water intake was measured to evaluate hydration status and potential renal or metabolic effects. A measured volume of fresh tap water was supplied to each cage daily using calibrated water bottles. After 24 hours, the remaining water volume was precisely measured using a graduated measuring cylinder. The daily water intake (in milliliters) for each group was calculated using the formula: Water Intake (mL) = [Initial Water Volume (mL)] – [Volume of Leftover Water (mL)].

2.3 Sample Collection and Biochemical Analysis

2.3.1 Euthanasia and Sample Collection

Following the experimental period, all animals were humanely euthanized using an overdose of ketamine hydrochloride (administered intraperitoneally at 0.5 mL). Following confirmation of deep anesthesia and cessation of vital signs, a midline thoracotomy was performed using a sterile dissecting set. Blood samples were collected via cardiac puncture using a 5 mL syringe and dispensed into appropriately labelled plain sample bottles corresponding to each experimental group. The collected blood was allowed to clot at room temperature and centrifuged at 3000 rpm for 10 minutes to separate the serum. The serum was carefully aspirated and aliquoted for the analysis of relevant plasma and cardiac biomarkers.

Immediately following blood collection, the heart was excised from each rat, rinsed in ice-cold phosphate-buffered saline (PBS), blotted dry, and weighed. The cardiac tissue was then homogenized in a cold phosphate buffer (pH 7.4) using a mechanical

homogenizer. The resulting homogenate was centrifuged at 2000 rpm for 15 minutes at 4°C. The clear supernatant was collected into fresh, labelled plain bottles and stored at -80°C until analysis for cardiac antioxidant markers.

2.3.2 Biochemical Assay Procedures

A. Determination of Glutathione (GSH)

The concentration of reduced glutathione (GSH) in the cardiac homogenate supernatant was quantified using a standard colorimetric assay, based on the reaction of GSH with 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to yield a yellow-colored 5-thio-2-nitrobenzoic acid (TNB). The procedure was conducted as follows:

- 100 µL of the sample or GSH standard was pipetted into a microcuvette.
- 880 µL of GSH dilution buffer was added to the microcuvette.
- 20 µL of the chromogen (DTNB reagent) was added, and the solution was mixed thoroughly.
- The absorbance of the resulting yellow solution was measured spectrophotometrically at a wavelength of 412 nm within 5 minutes of adding the chromogen.

B. Determination of Glucose-6-Phosphate Dehydrogenase (G6PDH) activity

The activity of Glucose-6-Phosphate Dehydrogenase (G6PDH) was assayed using a commercial Enzyme-Linked Immunosorbent Assay (ELISA) kit following the manufacturer's protocol. The microplate procedure was as follows:

- Coating and Incubation**:** 100 µL of standard or sample was added to each well of the pre-coated microplate and incubated for 90 minutes at 37°C.
- Washing and Addition of Detection Antibody**:** The liquid was aspirated, and each well was washed three times with wash buffer. Subsequently, 100 µL of biotinylated detection antibody was added to each well, followed by incubation for 1 hour at 37°C.
- Washing and Addition of Conjugate: After aspiration and a second cycle of three washes, 100 µL of Horseradish Peroxidase (HRP) conjugate was added to each well. The plate was incubated for 30 minutes at 37°C.
- Final Washing and Substrate Reaction: The wells were aspirated and washed thoroughly five times. Then, 90 µL of Tetramethylbenzidine (TMB) substrate reagent was added to each well and incubated for 15 minutes at 37°C in the dark to allow color development.
- Reaction Termination and Reading: The enzymatic reaction was stopped by adding 50 µL of stop solution to each well. The absorbance of the solution in each well was measured immediately at 450 nm using a microplate reader.
- Calculation: The G6PDH concentration in the samples was determined by interpolating their absorbance values against the standard curve generated from the known standards.

2.3 Determination of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Concentration

- The concentration of NADPH in the cardiac homogenate supernatant was quantified using a competitive Enzyme-Linked Immunosorbent Assay (ELISA) technique. The procedure was conducted as follows:
- Coating and Incubation: 100 µL of the NADPH standard or sample supernatant was aliquoted into each well of the pre-coated microplate. The plate was sealed and incubated for 90 minutes at 37°C.
- Washing and Addition of Detection Antibody: After incubation, the liquid was completely removed from the wells. Subsequently, 100 µL of biotinylated detection antibody specific to NADPH was added to each well. The plate was incubated for a further 60 minutes at 37°C.
- Washing and Addition of Conjugate: The solution was aspirated, and each well was washed three times with the provided wash buffer. Following this, 100 µL of Horseradish Peroxidase (HRP) conjugate was added to each well, and the plate was incubated for 30 minutes at 37°C.
- Final Washing and Substrate Reaction: After a second round of aspiration, the wells were washed five times with wash buffer. Then, 90 µL of TMB (3,3',5,5'-Tetramethylbenzidine) substrate reagent was added to each well. The plate was incubated in the dark for 15 minutes at 37°C to allow for color development proportional to the NADPH concentration.
- Reaction Termination and Reading: The enzymatic reaction was stopped by adding 50 µL of stop solution (acidic solution) to each well, which changed the color from blue to yellow. The absorbance was measured immediately at 450 nm using a microplate reader.
- Calculation: The concentration of NADPH in the samples was determined by interpolating the mean absorbance values against a standard curve generated from the known NADPH standards.

2.4 Determination of Glutathione Peroxidase (GPx) Activity

The activity of Glutathione Peroxidase (GPx) was assayed using a coupled enzymatic reaction that monitors the oxidation of NADPH at 340 nm. The procedure was performed as follows:

- Reaction Mixture Preparation: A master reaction mixture was prepared in a cuvette or microplate well, containing the following

components: appropriate assay buffer, reduced glutathione (GSH), nicotinamide adenine dinucleotide phosphate (NADPH), glutathione reductase (GR), and a defined volume of the sample supernatant containing GPx.

- Mixing and Initiation: The reaction mixture was mixed thoroughly and allowed to equilibrate. The reaction was initiated by adding a known, standardized quantity of hydrogen peroxide (H_2O_2), the substrate for GPx, to the mixture.
- Kinetic Measurement: The decrease in absorbance due to the oxidation of NADPH to $NADP^+$ was monitored spectrophotometrically at a wavelength of 340 nm. The initial linear rate of change in absorbance (ΔA/min) was recorded over a defined period of 1-3 minutes.
- Blank Correction: A control (blank) reaction was performed concurrently using a mixture where the sample was replaced with an equal volume of assay buffer. This reading accounted for any non-enzymatic oxidation of NADPH.
- Calculation of Results: GPx activity in the sample was calculated based on the observed rate of NADPH oxidation, after subtracting the blank rate. Activity was expressed in units per milligram of protein (U/mg protein), where one unit of GPx is defined as the amount of enzyme that oxidizes 1 µmol of NADPH per minute under the specified assay condition.

3. RESULTS

All data was expressed as mean + SEM. Statistical group analysis and group chart was performed with Graph pad prism (Version 8.01). One way analysis of variance (ANOVA) was used to compare the mean values of variables among the group. Statistically significant differences were accepted at $p<0.05$.

3.1. Effect of Vitamin D3 (Cholecalciferol) on Feed Intake in Male Wistar Rats Fed a High Sucrose Diet

The analysis of feed intake revealed significant alterations among the experimental groups. Data indicated a statistically significant increase ($p < 0.05$) in feed intake in both the Vitamin D3-only group and the Sucrose-only group when compared to the Control group. Conversely, a statistically significant decrease ($p < 0.05$) in feed intake was observed in the Sucrose + Vitamin D3 co-administered group relative to the Control. This pattern of results suggests that Vitamin D3 and a high-sucrose diet, when administered independently, stimulate appetite and increase food consumption. The observed hyperphagia in the Sucrose-only group may be attributed to sucrose-induced redox imbalance, which can disrupt normal glucose homeostasis and insulin signaling. Such dysregulation often leads to fluctuations in blood sugar levels, which can trigger hunger signals and subsequently result in increased feed intake. The significant reduction in feed intake in the co-treatment group implies a potential modulatory or interactive effect between Vitamin D3 and high dietary sucrose, counteracting the hyperphagic effect seen when either is administered alone

Table 2: The Effect of Vitamin D3 (Cholecalciferol) on Weekly Feed Intake (g) in Sucrose-Induced Male Wistar Rats

Groups	Feed intake(g)
Control	144.9± 5.9
Sucrose	148.63 ± 7.606*
Vitamin D3	156.96 ± 5.368*
Sucrose + Vitamin D3	130.8± 5.19#

Footnote: Values are expressed as Mean ± SEM. $p < 0.05$ vs. control group; #$p < 0.05$ vs. sucrose-only group.

3.2 Effect of Vitamin D3 (Cholecalciferol) on Water Intake in Male Wistar Rats Fed a High Sucrose Diet

The analysis of water intake revealed significant variations among the experimental groups. The data indicated a statistically significant increase ($p < 0.05$) in water consumption in both the Sucrose-only group and the Sucrose + Vitamin D3 co-administered group when compared to the Control group. This finding implies that a high-sucrose diet stimulates polydipsia, or increased water intake, in male Wistar rats. This physiological response may be attributed to the metabolic changes induced by high sucrose consumption, which can alter fluid balance and plasma electrolyte levels. Such disturbances, potentially including hyperglycaemia and osmotic diuresis, are known to influence thirst mechanisms via osmoreceptors and volume regulation, thereby leading to increased voluntary water intake.

Table 3: The Effect of Vitamin D3 (Cholecalciferol) on Weekly Water Intake (mL) in Sucrose-Induced Male Wistar Rats

Groups	Water intake(ml)
Control	159.3 ± 33.2

Sucrose	261.7 ± 16.9*
Vitamin D3	205.23 ± 6.32#
Sucrose + Vitamin D3	242.2 ± 8.95*

Footnote: Values are expressed as Mean ± SEM. *p < 0.05 vs. control group; #p < 0.05 vs. sucrose-only group.

3.3 Effect of Vitamin D3 on Plasma NADPH on Cardiac Redox Homeostasis of Male Wistar Rats Fed High Sucrose Diet

There was a significant increase in plasma NADPH levels of vitamin D3 group when compared to the sucrose group, and the control group. Plasma NADPH reduced significantly in the sucrose group compared to control. However, there was no significant difference in plasma NADPH of the control group and sucrose + vit. D3 group when compared (Figure 1)

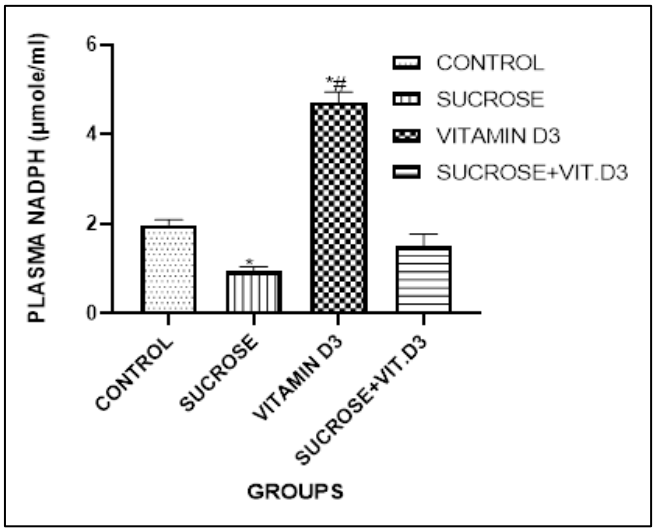

Figure 1: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet (*p<0.05 vs CTR, #p<0.05 vs S)

3.4 Effect of Vitamin D3 on Cardiac NADPH in Cardiac Redox Homeostasis in Male Wistar Rats Fed a High Sucrose Diet

Cardiac NADPH decreased significantly in the sucrose group compared to the control group. There was a significant increase in cardiac NADPH levels in vitamin D3 group when compared to control group, and sucrose group. Cardiac NADPH had no significant difference when sucrose + vit. D3 group was compared to control group. However, there was a significant increase in cardiac NADPH when sucrose + vit. D3 group compared to sucrose group.

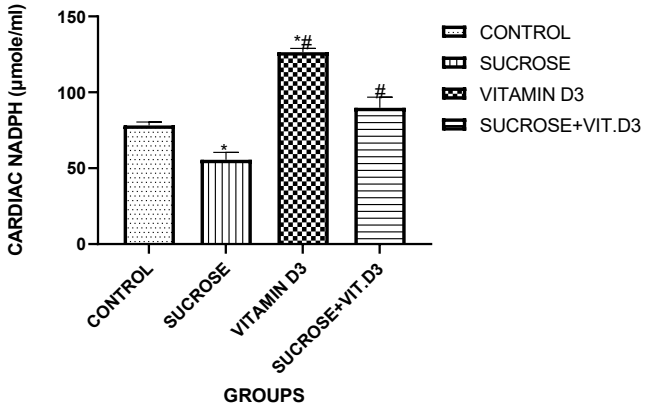

Figure 2: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet (*p<0.05vs CTR, #p<0.05 vs S)

3.5 Effect of Vitamin D3 on Plasma Glucose-6-Phosphate Dehydrogenase (G6PDH) in Male Wistar Rats Fed a High Sucrose Diet

There was a significant increase in plasma G6PDH levels in vitamin D3 group when compared to control group. Plasma G6PDH increased significantly in the vitamin D3 group compared to sucrose group.

However, no significant difference was observed in plasma G6PDH levels when sucrose group, and sucrose + vitamin D3 group were compared to control group.

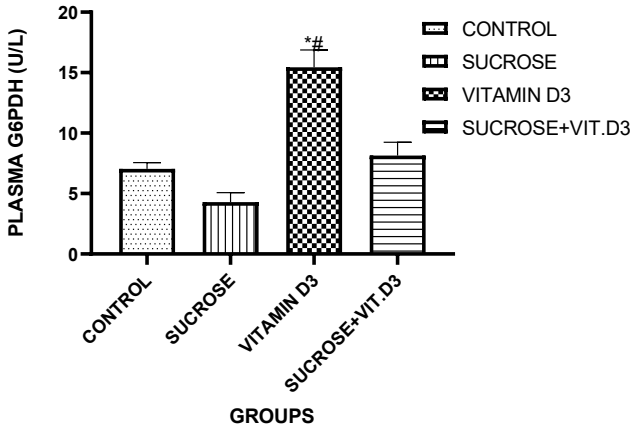

Figure 3: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet (*p<0.05 vs CTR, #p<0.05 vs S)

3.6 Effect of Vitamin D3 on Cardiac Glucose-6-Phosphate Dehydrogenase (G6PDH) in Male Wistar Rats Fed a High Sucrose Diet

Cardiac G6PDH decreased significantly in the sucrose group compared to the control group. There was a significant increase in cardiac G6PDH levels in vitamin D3 group when compared to the sucrose group. Cardiac G6PDH increased significantly in sucrose + vit. D3 group compared to sucrose group. However, there was no significant difference in cardiac G6PDH when vitamin D3 group, and sucrose + vitamin D3 group were compared to control group.

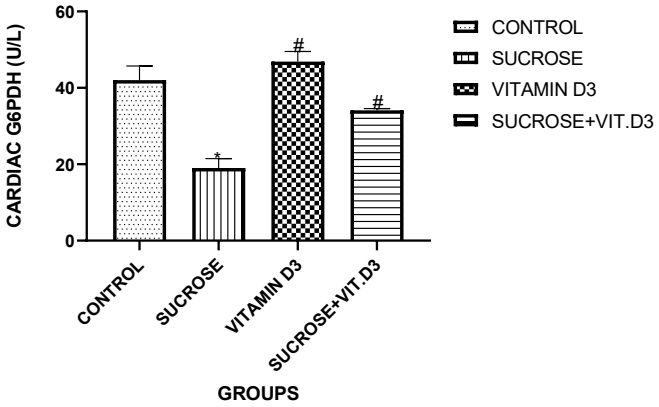

Figure 4: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet (*p<0.05vs CTR, #p<0.05 vs S)

3.7 Effect of Vitamin D3 on Plasma Glutathione (GSH) in Male Wistar Rats Fed a High Sucrose Diet

Plasma GSH decreased significantly in the sucrose group compared to control group. There was a significant increase in plasma GSH levels in vitamin D3 group when compared to control group, and sucrose group. However, there was no significant difference in plasma NADPH when sucrose + vitamin D3 group was compared to sucrose group, and control group.

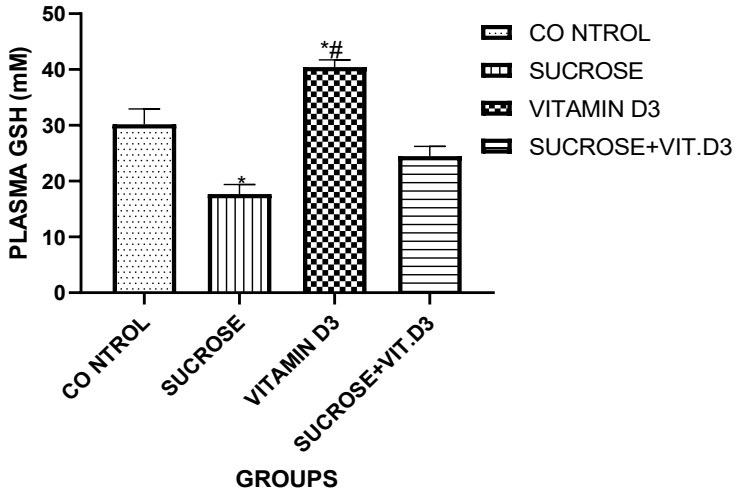

Figure 5: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet (*p<0.05 vs CTR, #p<0.05 vs S)

3.8 Effect of Vitamin D3 on Cardiac Glutathione (GSH) in Male Wistar Rats Fed a High Sucrose Diet

Cardiac GSH decreased significantly in the sucrose group compared to the control group. There was a significant increase in cardiac GSH levels in vitamin D3 group when compared to control group, and sucrose group. Cardiac GSH increased significantly in sucrose + vitamin D3 group compared to sucrose group. However, there was no significant difference in cardiac GSH when sucrose + vitamin D3 group was compared to control group.

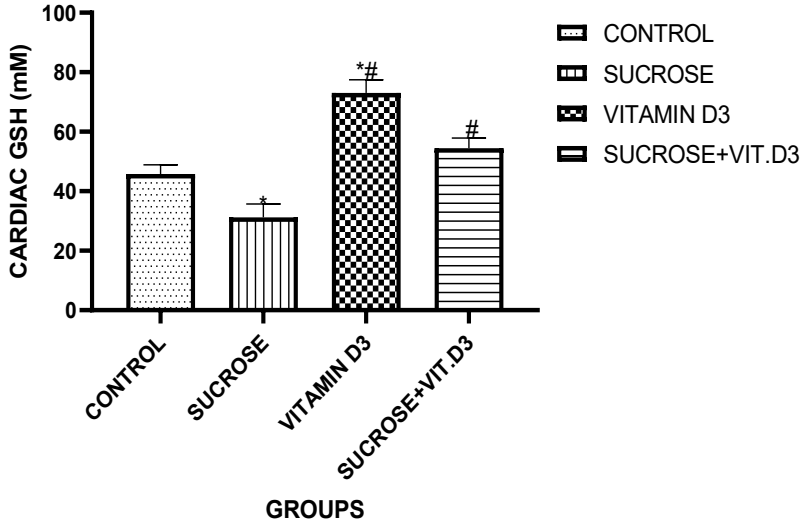

Figure 6: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet (*p<0.05vs CTR, #p<0.05 vs S)

3.9 Effect of Vitamin D3 on Plasma Glutathione Peroxidase (GPx) Activity in Male Wistar Rats Fed a High Sucrose Diet

Plasma GPx decreased significantly in the sucrose group compared to the control group. There was a significant increase in plasma GPx levels in Vitamin D3 group when compared to control group, and sucrose group. Plasma GPx increased significantly in sucrose +Vitamin D3 group compared to Sucrose group. However, there was no significant difference in plasma GPx when Sucrose + Vitamin D3group was compared to control group.

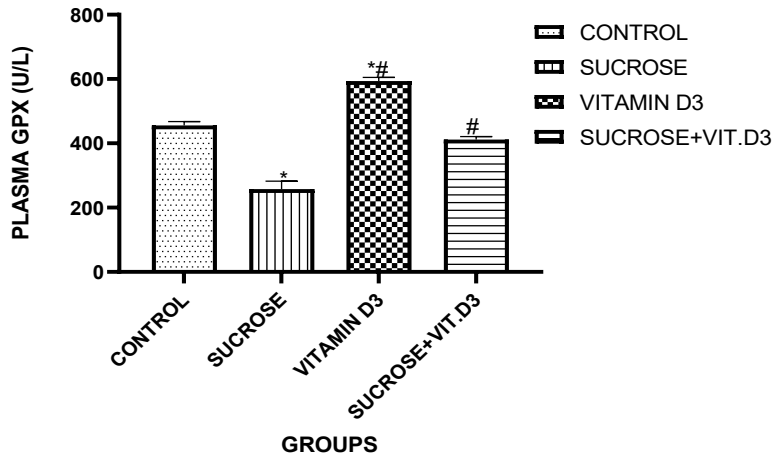

Figure 7: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed high sucrose diet (*p<0.05 vs CTR, #p<0.05 vs S)

3.10 Effect of Vitamin D3 on Cardiac Glutathione Peroxidase (GPx) Activity in Male Wistar Rats Fed a High Sucrose Diet

There was a significant increase in cardiac GPX levels in vitamin D3 group when compared to control group, and sucrose group. Cardiac GPX increased significantly in sucrose + vitamin D3 group compared to control group, and sucrose group. However, there was no significant difference in cardiac GPX when sucrose group was compared to control group.

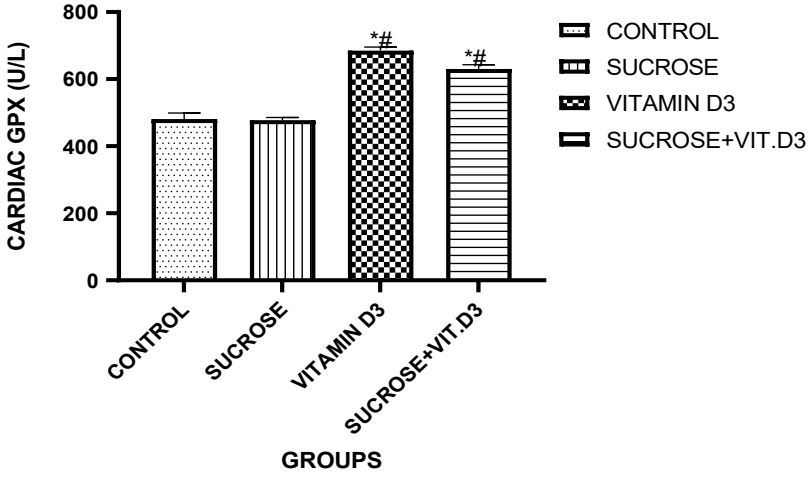

Figure 8: Effect of vitamin D3 on cardiac redox homeostasis in male Wistar rats fed a high sucrose diet (*p<0.05vs CTR, #p<0.05 vs S)

4. DISCUSSION

The present study showed that vitamin D3 ameliorated oxidative stress resulting from an imbalance in redox homeostasis induced by a high-sucrose diet by increasing plasma and cardiac NADPH, G6PDH, GSH, and GPX. In Figures 1 and 2, a high-sucrose diet reduced plasma and cardiac NADPH compared with control. Vitamin D3 was observed to increase plasma and cardiac NADPH. NADPH is a reducing equivalent that maintains catalase in the active form and is used as a cofactor by TRX and GSH reductase, which converts GSSG to GSH, a co substrate for the GSH-pxs (Dickson & Forman, 2002).

Additionally, the current study showed that compared to the control group, a high sucrose diet caused a significant decrease in plasma and cardiac G6PDH. Vitamin D3 caused a significant increase in plasma and cardiac G6PDH compared to control. G6PDH participates in the pentose phosphate pathway, a metabolic pathway that supplies reducing energy to cells by maintaining the level of the co-enzyme nicotinamide adenine dinucleotide phosphate (NADPH). The NADPH in turn maintains the level of glutathione in these cells that helps protect the red blood cells against oxidative damage from compounds like hydrogen peroxide (Yang *et al*., 2016).

In Figure 5 and 6, a high sucrose diet significantly reduced plasma and cardiac GSH. This is in accordance with a study carried out by Sadowska *et al*., 2012. Dietary sucrose, as opposed to complex carbohydrates, may have a differential effect on net oxidative stress and these differences are reflected in the accumulation of advanced glycation products (Maillard reaction) (McDonald, 2008). Although the mechanism accounting for this increased oxidative damage is yet to be elucidated, it appears that the fructose moiety of the sucrose molecule plays a larger role than the glucose moiety. A high-fructose diet stimulates de novo lipogenesis, it increases the hepatic VLDL secretion and decreases the peripheral triglyceride clearance (Watson *et al*., 2003). A diet rich in sucrose could alter cellular metabolism via several pathways and thereby increase oxidative stress.

Administration of vitamin D3 caused a significant increase in plasma and cardiac GSH levels when compared to control. (Figure. 5, and Figure.6). A study by Sedidarkish *et al*., 2019 showed that administration of vitamin D3 increased cellular glutathione levels. Vitamin D3 could enhance the pathway of ROS removal, by increasing the intracellular pool of GSH partially through upstream regulation of glutamate- cysteine ligase (GCL) and glutathione reductase gene expression. Development and progression of cardiovascular diseases are characterised by substantial changes in the concentration of GSH. GSH is the principal intracellular antioxidant which may act directly by scavenging reactive oxygen and nitrogen species or indirectly by supporting enzymatic activity as a cofactor (Gaucher *et al*., 2018).

GSH plays an important role in the cardiovascular, it restores intracellular redox equilibrium and prevents the inactivation of nitric oxide produced by the endothelium, leading to the aberrant vasomotor reactivity in individuals with coronary spastic angina (Kugiyama *et al*., 2001). Increased oxidation by intracellular oxidizing agents, increased conjugation to proteins, electrophiles, and xenobiotics, and increased extrusion across the cell membrane have been proposed to be involved in GSH dimunition (Franco *et al*., 2007; Espinosa-Diez *et al*., 2018; Deponte, 2017). In Figure 7, and Figure 8, a high sucrose diet caused a reduction in plasma GPX levels compared to control. Vitamin D3 on the other hand caused a significant increase in plasma and cardiac GPX in accordance with a study carried out by Pittas *et al*., 2019.

Glutathione peroxidase catalyzes the detoxification of hydrogen peroxide (H2O2) and lipid peroxides by reduced glutathione. Thus, it protects membrane lipids and hemoglobin from peroxide-mediated oxidation. GPx is also involved in the detoxification of xenobiotics. It is the antioxidant enzyme system that provides the most vital defence against the peroxidative damage of biological membranes in mammalian cells. From these enzymes, glutathione peroxidase, catalase, and superoxide dismutase together form a standard system aimed at protecting the cell from molecules (Colak *et al*., 2015).

5. CONCLUSION AND RECOMMENDATION

5.1 CONCLUSION

The findings from this study demonstrate that Vitamin D3 (Cholecalciferol) exerts significant cardioprotective effects in a high sucrose-diet model. This protection is mediated primarily through the upregulation of key components of the endogenous antioxidant defense system within cardiac tissue. Specifically, Vitamin D3 administration effectively counteracted sucrose-induced oxidative stress by increasing reduced glutathione (GSH) levels and the activities of critical antioxidant enzymes, including glutathione peroxidase (GPx) and glucose-6-phosphate dehydrogenase (G6PDH), while also supporting the availability of the essential cofactor NADPH. These collective actions contribute to the restoration and maintenance of cardiac redox homeostasis.

5.2 Recommendations

Based on the findings of this research, the following recommendations are proposed:

- Dose-Response and Long-Term Studies: To fully delineate the therapeutic window and potential risks, further studies are necessary. These should investigate higher doses of Vitamin D3 (exceeding 1500 IU/kg) administered over extended periods to establish a comprehensive dose-response profile and to ascertain any potential cardiotoxic effects that may arise at supraphysiological doses.
- Investigation of Molecular Mechanisms: Subsequent research should focus on elucidating the precise molecular pathways through which Vitamin D3 modulates antioxidant gene expression (e.g., via the Nrf2-Keap1 pathway) and enzyme activity in the myocardium to provide deeper mechanistic insight.
- Clinical Correlation: Translational studies are recommended to explore the implications of these findings in preclinical models of metabolic syndrome and diabetes, to inform potential adjuvant therapeutic strategies for patients with diet-induced cardiometabolic disorders.

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