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Original Article

Ameliorative Effects of D-Ribose-L-Cysteine on Hematological Indices and Metabolic Intermediates in Diabetic Male Wistar Rats

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic disorder characterized by hyperglycemia, insulin resistance, oxidative stress, and progressive β-cell dysfunction. Hematological parameters and metabolic intermediates often reflect systemic inflammation, immune competence, mitochondrial activity, and redox balance, all of which are perturbed in diabetes. This study evaluated the effects of D-ribose-L-cysteine (DRLC), a glutathione precursor, on hematological indices and selected intermediates of energy metabolism in male Wistar rats exposed to a High-Fat Diet (HFD) and Streptozotocin (STZ) (HFD+STZ).

Methods: Animals were randomly divided into control, HFD+STZ, HFD+STZ+DRLC (150 and 300 mg/kg), and HFD+STZ+metformin (100 mg/kg) groups. Treatments were administered orally for 28 days. Hematological indices (White Blood Cells (WBC), Lymphocytes (LYM), Hemoglobin (Hb), Red Blood Cells (RBCs), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), and metabolic intermediates (pyruvate, succinate, lactate) together with Malate Dehydrogenase (MDH) activity were assessed.

Results: The HFD+STZ group developed significant leukocytosis, lymphocytosis, anemia, elevated MCV, reduced pyruvate and succinate, increased lactate levels, and altered MDH activity compared to controls ($p<0.05$). DRLC administration significantly reversed these alterations in a dose-dependent manner, comparable to metformin. DRLC improved red blood cell integrity, enhanced hemoglobin levels, normalized energy metabolites, and modulated MDH activity, suggesting potent antioxidant and hemato-protective actions mediated through glutathione - dependent pathways.

Conclusion: DRLC effectively ameliorated hematological and mitochondrial derangements in diabetic rats, highlighting its therapeutic potential in mitigating diabetes-associated complications.

Keywords: *D-Ribose-L-Cysteine, Hematological Indices, Energy Metabolism Intermediates, Streptozotocin -Induced Diabetes, High-Fat Diet*

1. Introduction

Besides disturbances in glucose and lipid metabolism that are the hallmark of type 2 diabetes mellitus (T2DM), there are significant alterations in hematological parameters, reflecting systemic inflammation and oxidative stress associated with chronic hyperglycemia [1]. Hematological parameters often reflect systemic inflammation, immune competence, and overall physiological stress, while metabolic intermediates such as succinate, lactate, and pyruvate serve as indicators of mitochondrial function, glycolytic flux, and shifts in oxidative metabolism [2, 3]. In diabetic pathophysiology, disturbances in these biomarkers may reveal underlying mitochondrial dysfunction, altered redox status, and energy deficits [4]. Persistent high glucose levels promote non-enzymatic glycation of hemoglobin and other blood components, leading to changes in erythrocyte structure, lifespan, and oxygen-carrying capacity [1]. This often results in reduced Hb concentration and may contribute to the development of anemia commonly observed in diabetic individuals, particularly those with renal complications that impair erythropoietin synthesis [1-5].

White Blood Cell count is frequently elevated in diabetes, indicating a state of low-grade chronic inflammation. Hyperglycemia-induced oxidative stress activates inflammatory cytokines such as TNF-α and IL-6, which stimulate leukocytosis and enhance leukocyte adhesion to the endothelium. These immune responses, while initially protective, can exacerbate vascular injury and insulin resistance [6]. Conversely, in poorly controlled diabetes, immune dysfunction may also lead to leukopenia due to impaired bone marrow activity and increased apoptosis of leukocytes [7]. Similarly, lymphocyte count and function are adversely affected by metabolic dysregulation in diabetes. Chronic hyperglycemia alters lymphocyte proliferation, differentiation, and cytokine secretion, leading to immune suppression and increased susceptibility to infections [8]. Some studies have reported lymphopenia in diabetic patients, attributed to oxidative DNA damage and impaired antioxidant defense systems [9-11]. Reduced lymphocyte activity also contributes to the impaired wound healing and increased infection risk observed in diabetic individuals [12]. Among experimental models that replicate key facets of human T2DM, the combined HFD and low-dose STZ regimen has gained prominence for its reproducibility and translational relevance [13]. This model reliably induces metabolic derangements, including dyslipidemia, oxidative stress, and impaired glucose homeostasis, providing an ideal platform for evaluating therapeutic interventions [14, 15].

D-Ribose-L-cysteine (DRLC), a potent glutathione precursor, has emerged as a promising agent in mitigating oxidative and inflammatory insults across diverse disease states [16]. Its antioxidant and anti-inflammatory capacities have been demonstrated in rodents exposed to high-fat/high-fructose diets, where DRLC restored hepatic and systemic oxidative balance by enhancing superoxide dismutase (SOD), glutathione peroxidase (GPX), and total antioxidant capacity (TAC), while reducing markers like malondialdehyde (MDA), C-reactive protein (CRP), and xanthine oxidase (XO), [17, 18]. Parallel findings underscore its efficacy in preventing cardiometabolic syndrome and improving lipid and glucose homeostasis in rats fed a high-fat/high-fructose diet [19, 20].

In male Wistar rats rendered diabetic via STZ, DRLC normalized lipid profiles, attenuated oxidative stress markers, and enhanced reproductive hormone levels and sperm parameters [21-23]. These effects collectively underscore its multifaceted potential in ameliorating both systemic and organ-specific complications of diabetes. Despite these encouraging outcomes, a critical gap persists as the impact of DRLC on comprehensive hematological indices and intermediates of energy metabolism, including WBCs, LYM, Hb, RBC, MCV, MCHC, inorganic phosphate, succinate, lactate, and pyruvate, remains unexplored, particularly within the HFD-STZ rodent model. Therefore, investigating whether DRLC can exert ameliorative effects on both hematological indices and key metabolic intermediates in HFD-STZ-induced diabetic male Wistar rats is both timely and scientifically compelling. Such a study would deepen understanding of DRLC's mechanistic actions and its potential to restore hematological integrity and metabolic equilibrium in complex diabetic milieus.

2. Method

2.1 Equipment and Apparatus

Plastic cages (42 x 30 x 27 cm), needles, syringes, oral cannula, wash bottles, hand gloves, tissue homogenizer, sensitive electrical weighing balance (model JA 2003), cold centrifuge (AT KE), VIS spectrophotometer (model 722N), refrigerator, pH meter (Shanghai Weiye Instruments, China), micropipettes (REMI) 100-1000µl, mortar and pestle, cotton filter, 10 liters can, plastic bucket with cover, plain bottles and racks, test tubes, microplate ELISA reader, Eppendorf tubes, and beaker.

2.2 Animal care

Animals were obtained from the Laboratory Animal Centre of the College of Medicine, Delta State University, Abraka. Animals were acclimatized in the laboratory for ten days under normal standard conditions. All animals were allowed free access to water and feed.

2.3 Drugs and Chemicals

DRLC and STZ (Sigma-Aldrich, St. Louis, MO, USA), Sodium citrate buffer (0.1 M, pH 4.5) for STZ dissolution was prepared using citric acid and sodium citrate from Sigma-Aldrich (St. Louis, MO, USA). EDTA (ethylenediaminetetraacetic acid) as an anticoagulant for blood collection was sourced from Becton Dickinson (Franklin Lakes, NJ, USA). For hematological analysis of parame-

ters such as WBCs, LYM, Hb, RBCs, MCV, and MCHC, standard diluent and lysing reagents compatible with the Sysmex hematology analyzer were supplied by Sysmex Corporation (Kobe, Japan). The Succinate Colorimetric Assay Kit was obtained from Abcam (catalog no. ab204718; Cambridge, UK). The L-Lactate Assay Kit was sourced from Sigma-Aldrich (catalog no. MAK064; St. Louis, MO, USA). The Pyruvate Assay Kit was procured from Sigma-Aldrich (catalog no. MAK071; St. Louis, MO, USA). All other reagents and solvents were of analytical grade and purchased from Merck (Darmstadt, Germany) or Sigma-Aldrich (St. Louis, MO, USA) unless otherwise specified.

2.4 Experimental Diet

2.4.1 Purchase of Animal Feeds

Groundnut seeds were purchased from the local market in Abraka, Ethiope East Local Government Area, Delta State, Nigeria. Standard commercial pelleted feed was purchased from Rainbow Top Feed Company, Amukpe, Sapele, Delta State, Nigeria.

2.4.2 Identification

Groundnut seeds were identified and authenticated in the Department of Botany, Faculty of Science, Delta State University, Abraka, Nigeria, by Mr. Michael O.E

2.4.3 Preparation of High Fat Diet

Groundnut seed diet was prepared by the method described by a previous study [24]. The groundnut seeds were cleaned by removing stones and dirt and air-dried. The dried groundnut seeds were milled with the aid of a local manual grinder. The groundnut feed was properly stored to avoid contamination from pests and moulds. Throughout the course of the experiment, the diet was made twice a week to prevent the degradation of its concentration.

2.4.4 Composition of High Fat Diet

Eighty grams (80 g) of the milled Groundnut were added to 20 g of the normal commercial animal pellet to make a High Fat Diet.

2.4.5 Nutritional composition

Eighty grams (80 g) of the milled Groundnut were added to 20 g of the normal commercial animal pellet to make a high fat diet of nutrient composition below:

Table 1: Nutritional Composition Groundnut

Nutrient	Groundnut (80g)	Commercial feed (20g)	Total per 100g HFD	Energy contribution (Kcal)
Fat (g)	39.1	3.2	42.3	381 (9 kcal/g)
Carbohydrate (g)	19	10.8	29.8	119 (4 kcal/g)
Protein (g)	21.9	4.0	25.9	104 (4 kcal/g)
Total energy (kcal)	–	–	–	604 kcal/100 g

2.5 Experimental Design

Animals were fed an HFD for four weeks. On day 14 of the protocol, animals were injected with an initial dose of STZ 40 mg/kg intraperitoneally (IP) and a second dose on day 28 of the experimental protocol. Male Wistar rats weighing approximately 200-250 g were randomly divided into five groups (n=5). This sample size was consistent with similar experimental pharmacology studies. The control group was fed with a normal rodent diet. Group two was fed HFD-STZ, and groups three and four were administered HFD-STZ and graded doses of DRLC (150 mg/kg and 300 mg/kg *p.o*). Group five was administered HFD-STZ and the standard drug (metformin, 100 mg/kg BW) [16]. DRLC was prepared by dissolving 125 mg of DRLC in 12.5 ml of distilled water to obtain a stock solution of 10 mg/ml. The doses of STZ and composition of HFD that were used for this research work are based on a previous study [24]. Animals were treated for four weeks. DRLC was administered orally. At the end of the experimental protocol, animals were sacrificed by euthanasia. Blood samples were collected, and serum was obtained to determine the concentration of white blood cells, lymphocytes, hemoglobin, red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), inorganic phosphate, succinate, lactate, and pyruvate.

2.6 Hematological Analysis

The Sysmex XW-100 analyzer is factory-calibrated and does not require on-site calibration. System performance was verified through weekly instrument care and quality control procedures prompted by the analyzer software. Specimens producing unreliable results were automatically flagged. The analyzer is manufacturer-validated for EDTA-anticoagulated whole blood collected and stored under defined conditions, and only samples within the validated population and pre-analytical criteria were analyzed.

3. Results

3.1 Effect of D-ribose-L-cysteine on white blood cell count (WBC) in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on white blood cell count (WBC) is shown in Figure 1. One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant ($p<0.0$) increase in WBC count when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant $F(4,25) = 21.17$, $p<0.05$ decrease in WBC count when compared with the (HFD+ STZ) group only.

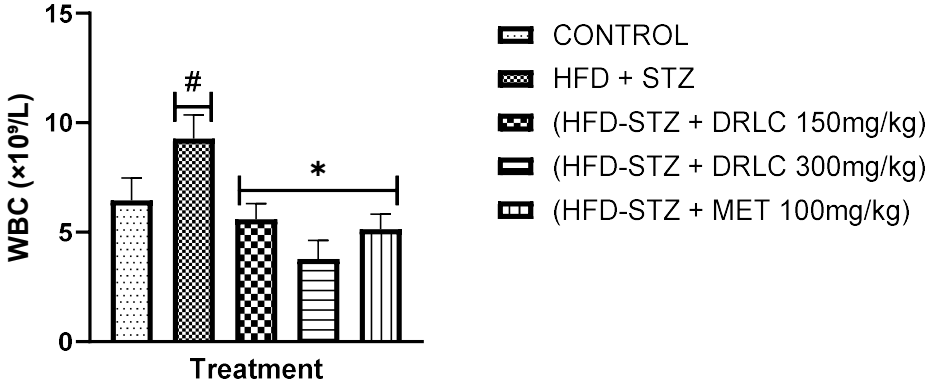

Figure 1: Effect of D-ribose-L-cysteine on white blood cell count (WBC) in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.2 Effect of D-ribose-L-cysteine on lymphocytes (LYM) in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on lymphocytes (LYM) is shown in Figure 2**.** One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant $F(4,25) = 25.72$, $p<0.05$ increase in LYM count when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant ($p<0.05$) decrease in LYM count when compared with the (HFD+ STZ) group only.

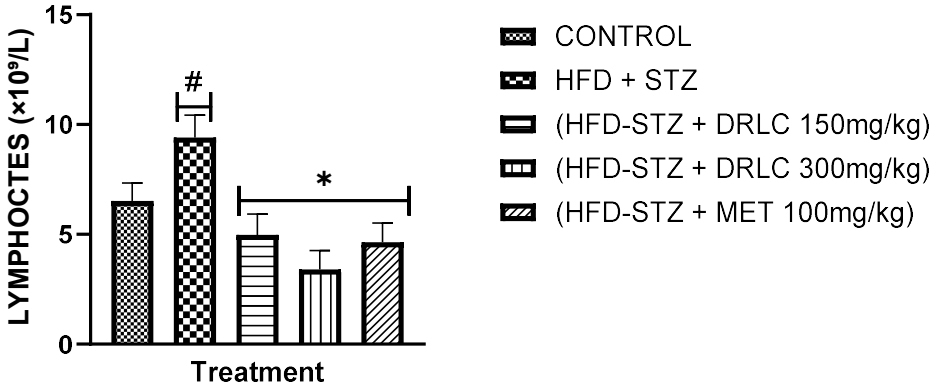

Figure 2: Effect of D-ribose-L-cysteine on lymphocytes (LYM) in rats exposed to STZ and HFD

Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.3 Effect of D-ribose-L-cysteine on Hemoglobin (Hb) in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on Hemoglobin (Hb) is shown in Figure 3**.** One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant $F(4, 25) = 43.70$, $p<0.05$ decrease in Hb levels when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant (p<0.05) increase in Hb levels when compared with the (HFD+ STZ) group only.

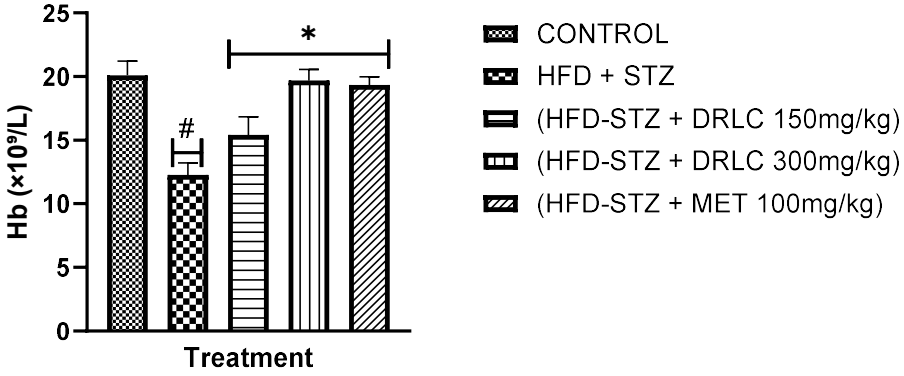

Figure 3: Effect of D-ribose-L-cysteine on Hemoglobin (Hb) in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control grozup (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.4 Effect of D-ribose-L-cysteine on red blood cell (RBC) in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on red blood cell (RBC) is shown in Figure 4**.** One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant $F(4,25) = 21.25$, $p<0.05$ decrease in RBC count when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant (p<0.05) increase in RBC count when compared with the (HFD+ STZ) group only.

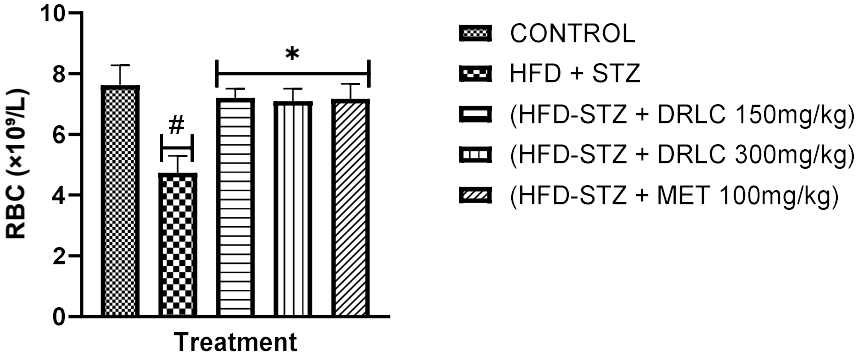

Figure 4: Effect of D-ribose-L-cysteine on red blood cell (RBC) in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.5 Effect of D-ribose-L-cysteine on** Mean Corpuscular Volume **(MCV) in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on mean corpuscular volume (MCV) is shown in Figure 5**.** One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant ($p<0.05$) increase in MCV levels when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant $F(4,25) = 25.16$, $p<0.05$ decrease in MCV levels when compared with the (HFD+ STZ) group only.

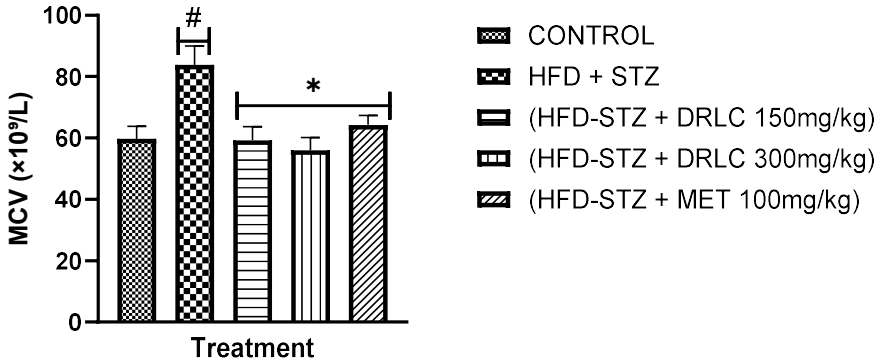

Figure 5: Effect of D-ribose-L-cysteine on Mean Corpuscular Volume in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.6 Effect of D-ribose-L-cysteine on** Mean Corpuscular Hemoglobin Concentration **(MCHC)in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on mean corpuscular hemoglobin concentration (MCHC) was shown in Figure 6. One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant ($p<0.05$) decrease in MCHC levels when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant $F(4,25)= 17.28$, $p<0.05$ increase in MCHC levels when compared with the (HFD+ STZ) group only.

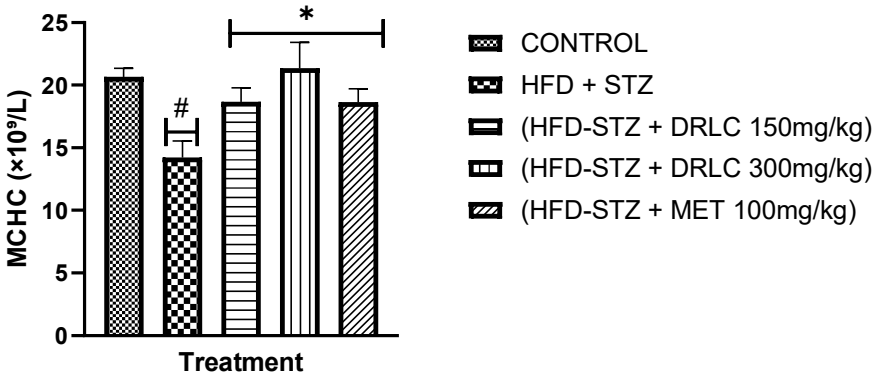

Figure 6: Effect of D-ribose-L-cysteine on Mean Corpuscular Hemoglobin Concentration in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.7 Effect of D-ribose-L-cysteine on** pyruvate levels **in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on pyruvate levels is shown in Figure 7**.** One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant $F(4,25) = 31.34$, $p<0.05$ decrease in pyruvate levels when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days

produced a significant ($p<0.05$) increase in pyruvate levels when compared with the (HFD+ STZ) group only.

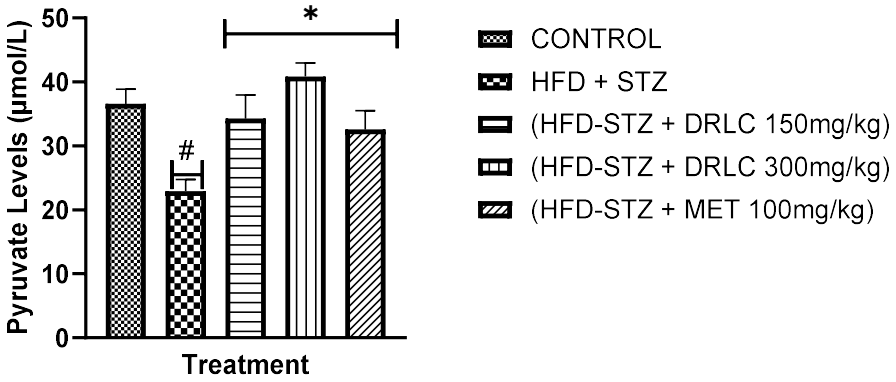

Figure 7: Effect of D-ribose-L-cysteine on pyruvate levels in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.8 Effect of D-ribose-L-cysteine on** Succinate levels **in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on succinate levels was shown in Figure 8. One-way ANOVA showed that there was a significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant $F(4,25) = 97.82$, $p<0.05$ decrease in succinate levels when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant ($p<0.05$) increase in succinate levels when compared with the (HFD+ STZ) group only.

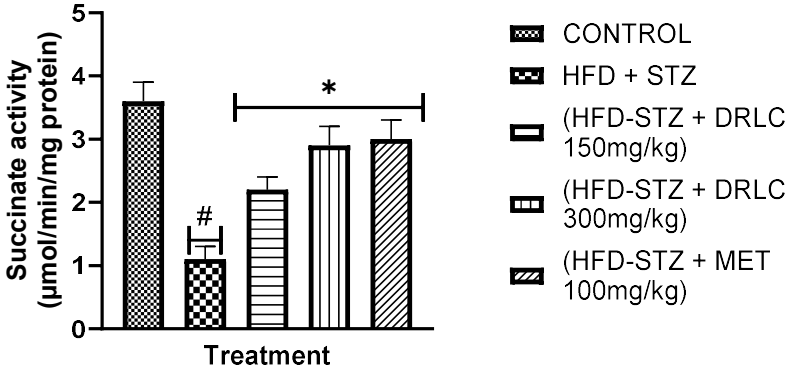

Figure 8: Effect of D-ribose-L-cysteine on Succinate levels in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.9 Effect of D-ribose-L-cysteine on** lactate levels **in rats exposed to STZ and HFD

The effect of D-Ribose-L-Cysteine given daily for 28 days on lactate levels is shown in Figure 9. One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant $F(4,25) = 30.34$, $p<0.05$ increase in lactate levels when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant ($p<0.05$) decrease in lactate levels when compared with the (HFD+ STZ) group only.

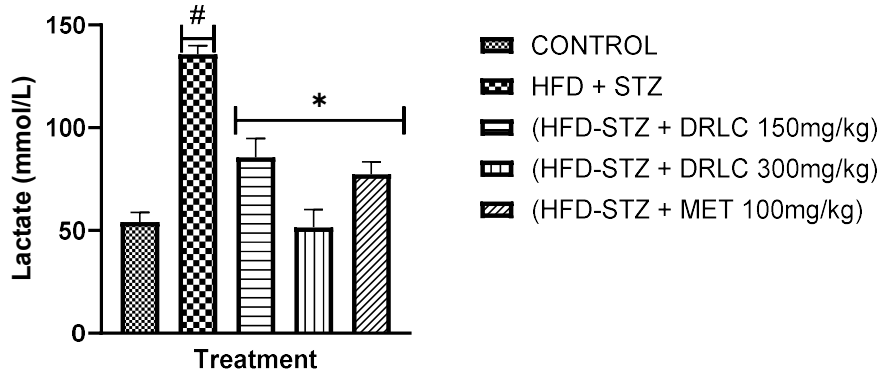

Figure 9: Effect of D-ribose-L-cysteine on lactate levels in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

3.10 Effect of D-ribose-L-cysteine on** Malate Dehydrogenase levels **in rats exposed to STZ and HFD
The effect of D-Ribose-L-Cysteine given daily for 28 days on malate dehydrogenase levels is shown in Figure 10. One-way ANOVA showed that there was significant difference between treatment groups. Post hoc analysis using Tukey's post hoc test revealed that the high fat diet and streptozotocin (HFD + STZ) group showed a significant $F(4,25)= 76.12$, $p<0.05$ decrease in malate dehydrogenase levels when compared to the control group, while DRLC (150, 300 mg/kg), metformin 100mg/kg, given daily for 28 days produced a significant ($p<0.05$) increase in malate dehydrogenase levels when compared with the (HFD+ STZ) group only.

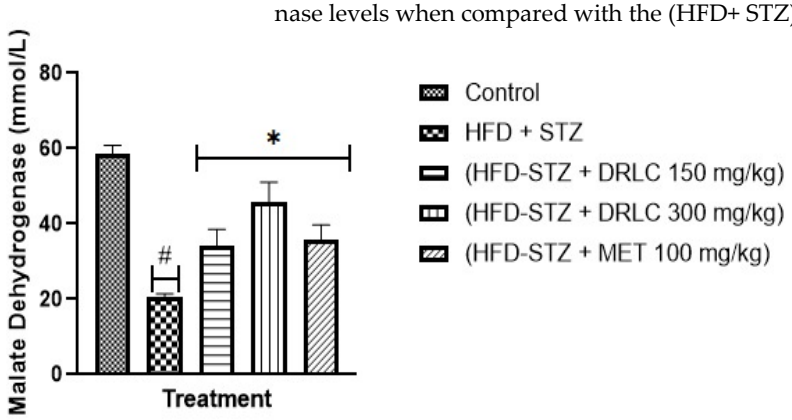

Figure 10: Effect of D-ribose-L-cysteine on malate dehydrogenase levels in rats exposed to STZ and HFD
Values represent the mean ± S.E.M for 5 animals per group
 # p<0.05 compared to the control group (ANOVA followed by Tukey's post hoc test).
** p<0.05 compared to the pathologic group (ANOVA followed by Tukey's post hoc test).*

4. Discussion
The provided results demonstrate the multifaceted therapeutic potential of D-Ribose-L-cysteine (DRLC) in ameliorating metabolic and hematological derangements in a rat model of type 2 diabetes (T2DM) induced by a high-fat diet (HFD) and streptozotocin (STZ). The current data specifically highlight DRLC's impact on red blood cell health and core energy metabolic pathways, suggesting a significant role in improving cellular bioenergetics. The study found a significant increase in both WBC count and lymphocyte count in the HFD+STZ group compared to the control. This is a crucial finding, as elevated white blood cell counts, particularly lymphocytes, are widely recognized as markers of systemic inflammation associated with metabolic syndrome, obesity, and type 2 diabetes [26-28]. Hyperglycemia, dyslipidemia, and visceral adiposity in the HFD+STZ model contribute to the activation of immune cells, leading to increased production of pro-inflammatory cytokines and infiltration of immune cells into various tissues [27-30]. Both DRLC (at 150 and 300 mg/kg) and metformin significantly reduced the elevated WBC and LYM counts in the HFD+STZ group. Metformin's anti-inflammatory properties are well-documented, extending beyond its glucose-lowering effects [31].

Furthermore, the HFD+STZ group exhibited a significant decrease in both Hb levels and RBC counts compared to the control group, thus indicating the development of anemia in the diabetic model. Anemia is a common complication in diabetic patients, often multifactorial in origin, involving impaired erythropoiesis, reduced erythrocyte lifespan due to oxidative damage and increased osmotic fragility, chronic inflammation, and sometimes nutritional deficiencies [32-33]. Hyperglycemia significantly contributes to oxidative stress in red blood cells, leading to their premature destruction (hemolysis) and decreased production (erythroid suppression), [34]. Chronic inflammation also suppresses erythropoiesis by altering iron metabolism and inhibiting erythropoietin production or response [35].

Remarkably, DRLC (both doses) and metformin significantly increased Hb levels and RBC counts when compared to the HFD+STZ group, effectively ameliorating the anemia. This protective effect aligns with their potential to reduce systemic inflammation and oxidative stress. By improving the antioxidant status via GSH synthesis, DRLC can protect red blood cells from oxidative damage, thereby prolonging their lifespan and improving erythropoiesis. Regarding mean corpuscular volume (MCV), the HFD+STZ group exhibited a significant increase in MCV compared to the control group. Elevated MCV values typically indicate macrocytic anemia, which can be associated with various conditions, including vitamin deficiencies (B12 and folate), liver disease, hypothyroidism, and occasionally chronic inflammatory states and oxidative stress [36]. In the context of diabetes, increased oxidative stress can lead to swelling and morphological changes in red blood cells, potentially contributing to an elevated MCV [34]. Both DRLC (150, 300 mg/kg) and metformin significantly decreased the elevated MCV levels back toward normal, compared to the HFD+STZ group.

Additionally, the HFD+STZ group exhibited a significant decrease in pyruvate and a corresponding significant increase in lactate levels. This metabolic signature is indicative of a shift toward anaerobic glycolysis and impaired oxidative phosphorylation [37, 38]. The decreased pyruvate suggests either reduced glycolytic flux leading to pyruvate or impaired utilization of pyruvate, while increased lactate points to inefficient aerobic respiration and a compensatory mechanism for ATP generation [39]. Moreover, the significant decrease in succinate levels in the HFD+STZ group provides further evidence of severe mitochondrial dysfunction. Succinate is a crucial intermediate of the tricarboxylic acid (TCA) cycle and also acts as a substrate for Complex II of the electron transport chain (succinate dehydrogenase), [40-41]. Reduced succinate levels directly imply a slowdown or impairment within the TCA cycle, which is central to aerobic energy production in the mitochondria [40-42]. Dysregulation of the TCA cycle and mitochondrial respiration is a hallmark of diabetes pathophysiology, leading to reduced ATP synthesis and accumulation of ROS [43].

5. Conclusion

Overall, these results strongly suggest that DRLC effectively counteracts the metabolic derangements induced by HFD+STZ, particularly by improving hematological parameters (WBC, LYM, Hb, RBC, and MCV), mitochondrial function and, possibly enhancing aerobic energy production. The observed improvements in metabolic intermediates (pyruvate, lactate, succinate, and malate dehydrogenase) further solidify that DRLC's shows promise as a therapeutic agent in mitigating diabetes-associated hematological and mitochondrial dysfunction.

Declarations

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Contribution of authors: IH and EAT, conceptualized and designed the study; IH and ACO did the experimental studies; EAT and ACO did the data analysis; IH, EAT, and BB did the original draft of the manuscript. All authors revised and approved the manuscript for submission.
Ethical approval: Before the commencement of the study, ethical approval (RBC/FBMC/DELSU/25/655) was sought from the Delta State University Animal Care and Use Research Ethics Committee of the Faculty of Basic Medical Sciences according to the directions from the National Institutes of Health Guide for Care and Use of Laboratory Animals.
Availability of data and materials: All data supporting the findings of this research work are included within the manuscript. Additional data related to this study are available from the corresponding author
Use of artificial intelligence (AI): All authors confirm that the writing of this manuscript is an original work and we that the use of artificial intelligence was not employed in the writing process
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