Acetate attenuates lipid peroxidation in streptozotocin-induced diabetes mellitus in male wistar rats

Dangana E.O.*[1,4], Negedu N.M[1], Ekpe C.A[1] Ben. E.E[1,2] Benjamin E,[3] Ogbe K.U[6], Tijani J.A[1,4] Michael E.O.[5]

[1]Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria.
[2]Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Uyo, Uyo, Akwa Ibom State, Nigeria
[3]HOPE Cardiometabolic Research Unit, University of Ilorin, Kwara State, Nigeria
[4]Cardio Metabolic Research and Awareness Foundation, Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria.
[5] Department of Accounting, Federal University, Lokoja, Kogi State, Nigeria
[6]Department of Plant Biology, Faculty of Natural Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria

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**Corresponding Author: Dangana Elizabeth Ojochebo; dangana.e@ksu.edu.ng*

Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, insulin resistance, and dyslipidemia, which contribute to lipid peroxidation. Although previous studies have shown a link between lipid peroxidation and diabetes, the potential therapeutic role of acetate remains unclear. This study examined the effects of sodium acetate on lipid peroxidation, glucose homeostasis, and oxidative stress in a streptozotocin-induced diabetic rat model.

Thirty male Wistar rats were randomly assigned to six groups (n = 5). Diabetes was induced using streptozotocin (65 mg/kg, i.p.), and rats with blood glucose ≥ 200 mg/dL after 72 hours were considered diabetic. The groups included control, diabetic untreated, acetate-treated (200 mg/kg, p.o.), metformin-treated (100 mg/kg, p.o.), diabetic + acetate, and diabetic + metformin. Treatments were administered daily for 21 days. Fasting glucose, insulin, lipid profile, and oxidative stress markers (MDA, FFA, GSH, GPx) were analyzed using standard biochemical assays.

Sodium acetate treatment significantly reduced elevated fasting glucose (≈ 35%), MDA (≈ 40%), and HOMA-IR values compared with diabetic controls ($p < 0.05$). Also, sodium acetate significantly improved lipid profile and antioxidant enzyme levels (MDA, FFA, GSH and GPx).

These findings suggest that sodium acetate may augment the effects of standard anti-diabetic drugs by attenuating lipid peroxidation and oxidative stress in diabetes mellitus.

Keywords: Acetate; lipid peroxidation; oxidative stress; diabetes mellitus

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from inadequate insulin production or impaired insulin sensitivity. It is one of the leading global causes of morbidity and mortality. Both genetic and environmental factors contribute to the development of type 2 diabetes, which accounts for over 90% of all cases. In 2021, the International Diabetes Federation (IDF) estimated that 537 million individuals were living with diabetes, representing 10.5% of the global population and adding substantially to the global healthcare burden (Magliano and Boyko, 2021; Olaniyi et al., 2021; Baek et al., 2018; Shaw et al., 2010).

Uncontrolled diabetes leads to long-term complications such as cardiovascular disease (CVD), neuropathy, nephropathy, and retinopathy, driven largely by metabolic imbalances and oxidative stress. Lipid peroxidation plays a pivotal role in the pathophysiology of diabetes, exacerbating oxidative stress and damaging cell membranes rich in polyunsaturated fatty acids. Hyperglycemia-induced oxidative stress disturbs the balance between reactive oxygen species (ROS) production and the antioxidant defense system, resulting in membrane damage and disease progression. Lipid peroxidation, marked by elevated malondialdehyde (MDA) levels, contributes to tissue injury (Sadi and Konat, 2020). Controlling oxidative stress through antioxidants and optimal glucose regulation can help mitigate these effects.

Metabolic dysregulation in diabetes also manifests as alterations in glucose and lipid homeostasis. Dyslipidemia, characterized by elevated total cholesterol, triglycerides, and decreased high-density lipoprotein (HDL) cholesterol, is a key feature contributing to cardiovascular complications (Luc et al., 2021). Effective regulation of glucose and lipid metabolism is therefore critical in the management of diabetes.

Sodium acetate, a salt of acetic acid and a short-chain fatty acid (SCFA), has been shown to influence metabolic pathways, improve glucose regulation, and modulate lipid metabolism (Olaniyi et al., 2020). Acetate, produced through microbial fermentation of dietary fiber in the gut, has been linked to several beneficial metabolic effects. Studies demonstrate that acetate can reduce oxidative stress, enhance antioxidant defenses (Hossain et al., 2023), and improve lipid metabolism (Dangana et al., 2020). It enhances insulin sensitivity and reduces blood glucose levels by activating G-protein-coupled receptors (GPCRs) involved in metabolic regulation (De Vadder et al., 2018). Moreover, acetate reduces cholesterol and triglyceride levels while increasing HDL cholesterol, suggesting a potential cardiometabolic advantage (Marques et al., 2016; Olaniyi et al., 2020).

Despite these findings, the precise role of sodium acetate in modulating lipid peroxidation and oxidative stress in diabetes remains unclear. While acetate's metabolic effects are known, its ability to augment the effects of standard anti-diabetic drugs and mitigate oxidative injury has not been fully explored.

Therefore, this study aims to evaluate the effects of sodium acetate on glucose regulation, lipid peroxidation, and oxidative stress in a streptozotocin-induced diabetic rat model.

Materials and methods

Animals, Equipment, Drugs and Reagent

Thirty (30) male Wistar rats weighing between 200–250g were used for this study. The rats were purchased and housed at the animal house of College of Health Sciences, Prince Abubakar Audu University, Anyigba, Kogi State under standard laboratory conditions with a 12-hour light/dark cycle with free access to feed and water. The animals were allowed to acclimatize for one week before the experiment. The rats were then randomly divided into six groups (n=5 per group) (Table 1). Streptozotocin (purchased from Macklin Biomedicals, France), 0.1M citrate-buffered saline (pH 4.5). The ELISA kits were purchased from Elab science.

Ethical considerations: All experimental procedures followed the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals and were approved by the Prince Abubakar Audu University animal care and ethics committee (CREC-CHS/PAAU/2025/0004).

Induction of diabetes

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 65 mg/kg after an overnight fast. Seventy-two hours (Ghasemi *et al.,*2023) after the STZ injection, fasting blood glucose levels were measured. Rats with blood glucose levels above 200 mg/dL were considered diabetic and included in the study.

Table 1: Animal grouping and their treatment

Groups/ n=5	Treatment	Dosage/ *po*
Control group (CTR)	Distilled water	10ml/kg
Diabetic group (DIA)	Diabetic with Distill water	10ml/kg
Sodium acetate group (ACE)	Non-diabetic rats treated with sodium acetate	200 mg/kg (Dangana et al., 2020)
Metformin group (MET)	Non-diabetic rats treated with metformin	100 mg/kg (Ben *et al*, 2023)
Diabetes + Metformin group (DIA+MET)	Diabetic rats treated with metformin	100 mg/kg
Diabetes + Sodium acetate group (DIA+ACE	Diabetic rats treated with sodium acetate	200 mg/kg

All treatments were given daily and lasted for 21 days.

Determination of the fasting blood glucose (FBG) level

Fasting blood glucose were measured every weeks (Days 7, 14 and 21) using a digital glucometer (Finetest glucometer, CodixPharmax, Nigeria). The tail of the rat was slightly cut using a scissors to expose the vein and a drop of blood was put on the glucometer strip attached to the glucometer. The reading was recorded in mg/dL for each rat (Ben et al, 2023).

Blood sample collection

Following 21 days treatment period, the rats were fasted overnight and then anaesthetized

with 50 mg/kg ketamine hydrochloride. Blood samples were collected via cardiac puncture in plain bottles and centrifuged at 3000 x g for 10 minutes to obtain plasma for biochemical assays.

Determination of insulin sensitivity status of the diabetic rats

Insulin level was measured using specie-specific enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instruction as described by Ben et al., 2023. HOMA-IR (Homeostatic Model Assessment of Insulin Resistance): Calculated using fasting glucose and insulin levels with the formula (Ben *et al.,* 2023, Dangana et al., 2020)

HOMA-IR = fasting insulin ((μU/mL)) × fasting glucose{(mg/dL) ÷ 405

Determination of lipid profile and free fatty acid

Lipid profile were measured using standard enzymatic colorimetric methods on plasma. Reagent systems for each analyte typically include:

- **Total cholesterol:** cholesterol esterase (CE) hydrolyses cholesteryl esters → free cholesterol. Cholesterol oxidase (CO) converts cholesterol → cholest-4-en-3-one + H_2O_2. In the presence of peroxidase (POD), H_2O_2 reacts with a chromogenic couple (e.g., 4-aminoantipyrine + phenol) to produce a quinoneimine dye measured at ~500 nm.
- **Triglycerides:** lipase converts triglycerides → glycerol; glycerol kinase (GK) phosphorylates glycerol → glycerol-3-phosphate; glycerol-3-phosphate oxidase (GPO) produces H_2O_2 which is detected via POD + chromogen to give a colored product read at ~500 nm.
- **HDL-C:** HDL was measured by direct homogeneous enzymatic assays using selective detergents that block non-HDL particles.
- **LDL-C:** calculated by the Friedewald formula (LDL-C = TC − HDL-C − TG/5) when TG < 400 mg/dL.

Assays were run according to the reagent manufacturer's instructions (reagent composition and incubation times vary by vendor); calibrators and controls were included on each run, and absorbance measured on a clinical chemistry analyzer or microplate reader. Use of established clinical laboratory reagent suppliers (e.g., Randox, Roche, Abbott) ensures validated reagent formulations and calibrations.

Free Fatty Acid: Assessed using an enzymatic colorimetric method (Kumar.,*et al.,* 2023, Rifai and Horvarth, 2023).

Determination of malondialdehyde (MDA):

Lipid peroxidation was quantified by measuring malondialdehyde (MDA) using the TBARS reaction. Samples (plasma) were deproteinized with 10% trichloroacetic acid (TCA) (v/v) and centrifuged at 3,000–5,000 × g for 10 min at 4 °C. The plasma (or appropriately diluted sample) was mixed 1:1 (v/v) with thiobarbituric acid (TBA) reagent (0.67% w/v TBA prepared in 50 mM acetic acid, pH ≈ 3.5). Butylated hydroxytoluene (BHT, 0.01% w/v) was added to buffers during sample preparation to prevent artifactual oxidation. The reaction mixtures were heated at 95–100 °C for 60 min in a sealed tube, cooled on ice for 10 min, and centrifuged to remove particulates. The pink MDA–TBA adduct absorbance was read at 532–535 nm in a spectrophotometer or

microplate reader. Quantitation was by comparison to an MDA standard curve (prepared from 1,1,3,3-tetraethoxypropane hydrolysed to MDA), and results expressed as nmol MDA per mg protein or per mL sample. For low-MDA samples, protocols that include n-butanol extraction (to concentrate the adduct) were used to improve sensitivity (O.J.,*et al.,*2023).

Determination of oxidative status of the diabetic rats

GSH (and total glutathione) was measured using a DTNB-based recycling assay (glutathione reductase/DTNB method). In brief, samples were prepared in appropriate buffer (e.g., phosphate buffer pH 7.5) and deproteinized when required (e.g., with 5% metaphosphoric acid) then neutralized. The assay uses 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB, Ellman's reagent) which reacts with reduced glutathione to form 2-nitro-5-thiobenzoic acid (TNB; yellow), and glutathione reductase together with NADPH to recycle oxidized glutathione (GSSG) back to GSH — amplifying the signal. Absorbance was measured at 412 nm (microplate reader) and concentration interpolated from a GSH standard curve. When separate measurement of GSSG was required, samples were pretreated with 2-vinylpyridine or N-ethylmaleimide to derivatize GSH and allow GSSG quantification after reduction. Follow kit-specific instructions for reagent volumes, incubation times, and dilution factors Also, Lactate and Lactate Dehydrogenase was determined by Enzymatic Spectrophotometric method (Zhao and Tu, 2023, Bergmeyer and Grass 2018).

Statistical analysis: Normality was assessed by the Shapiro–Wilk test and homogeneity of variances by Levene's test. Between-group comparisons were performed by one-way ANOVA (GraphPad Prism v10.0). Post-hoc pairwise comparisons used Tukey's multiple comparisons test. Statistical significance was accepted at $p < 0.05$." The data were expressed as mean ± standard deviation (SD).

Results

Fasting blood glucose and insulin levels in diabetic rats

The result showed a significant ($p< 0.05$) increase in the fasting blood sugar (figure 1a), plasma insulin (1b) and HOMA-IR levels in the diabetic rats compared to controls. However, diabetic treatment with sodium acetate (Dia+Ace) resulted in a significant ($p < 0.05$) decrease in blood glucose (figure 1a), insulin levels (Figure 1b) and HOMA-IR (Figure 1c).

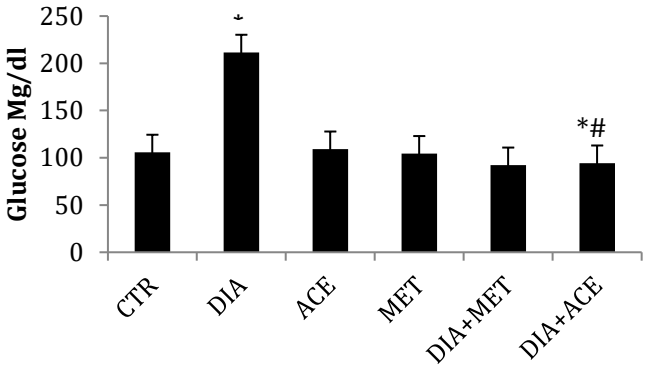
Effects of sodium acetate on lipid profile in diabetic rats

Diabetic rats showed significant increase ($p < 0.05$)in total cholesterol levels compared to the control however, diabetic with acetate (Dia+Ace) treatment showed significant decrease in the total cholesterol compared to the diabetic treated (figure 2a).Triglyceride levels were markedly increased in diabetic rats compared to controls, however, diabetic with sodium acetate administration significantly reduced ($p < 0.05$) triglyceride levels compared to the diabetic rats (figure 2b).HDL significantly decreased ($p < 0.05$) in diabetic group compared to the control however, diabetic with sodium acetate treated group significantly increased ($p < 0.05$) HDL compared to the diabetic group (Figure 2c).

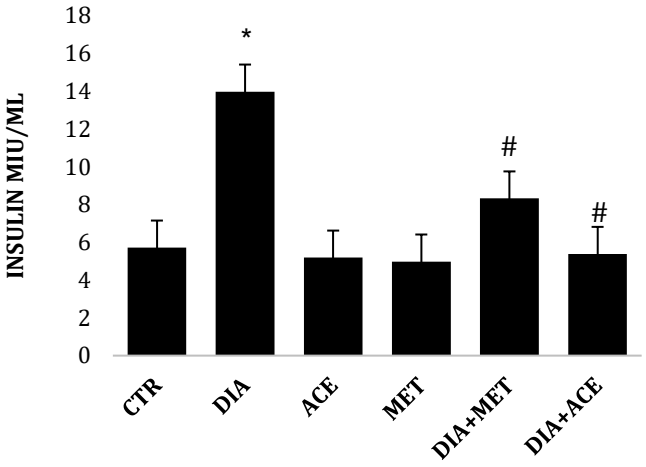
Effects on markers of lipid peroxidation and antioxidants

Diabetic rats compared to the control showed significant increase in MDA, however, diabetic with sodium acetate treatment compared to the diabetic rats showed significant decrease in the MDA (figure 3b). There was also significant increase ($p< 0.05$) in free fatty acid (figure 3a) in diabetic rats compared to the control but was significantly decreased ($p< 0.05$) in diabetic treated with sodium acetate compared to the diabetic rats (figure 3b). Also there was significant increase ($p< 0.05$) in lactate dehydrogenase in the diabetic group compared with the control however, diabetic with acetate treatment significantly decreased ($p< 0.05$) lactate dehydrogenase compared to the diabetic rats (figure 3c) Lactate level in the study was comparable (figure 3d). In addition, there was significant decrease ($p< 0.05$) in glutathione level and glutathione (figure 3f) peroxidase activities (figure 3e) compared to the control. However, diabetic with acetate treatment improved the Glutathione level and glutathione peroxidase activities compared to the diabetic rats.

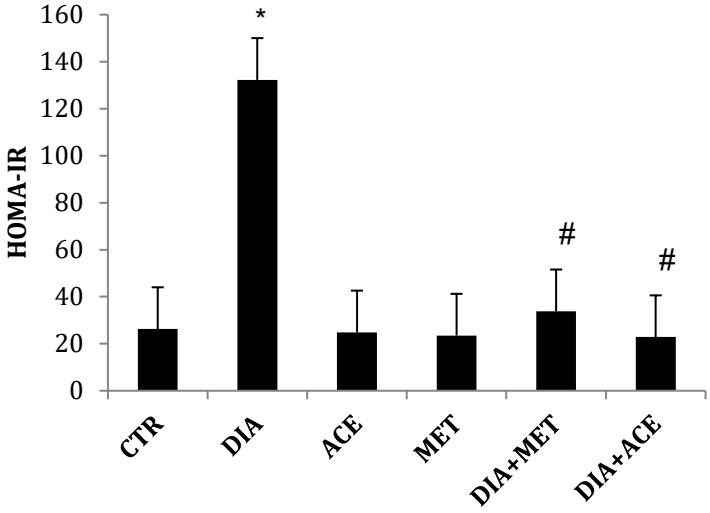
(a)



(b) CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate



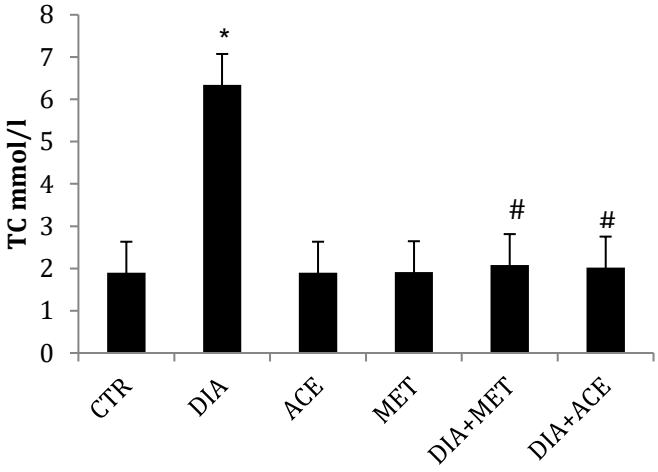
(c) CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate



CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate

Figure 1: Effect of Acetate on (a) blood glucose and (b) insulin in streptozoccin-induced diabetic rats. There was significant increase in blood glucose but decreased insulin level of diabetic rats compared to the control whereas diabetic plus acetate treated rats showed significant decrease in blood glucose. Data were analyzed by one-way ANOVA followed by Turkey's comparison *post hoc* test. Values are expressed as mean ± SEM of 5 rats per group. * DIA VS CTR P<0.05 # DIA+ACE VS DIA P<0.05

(a)



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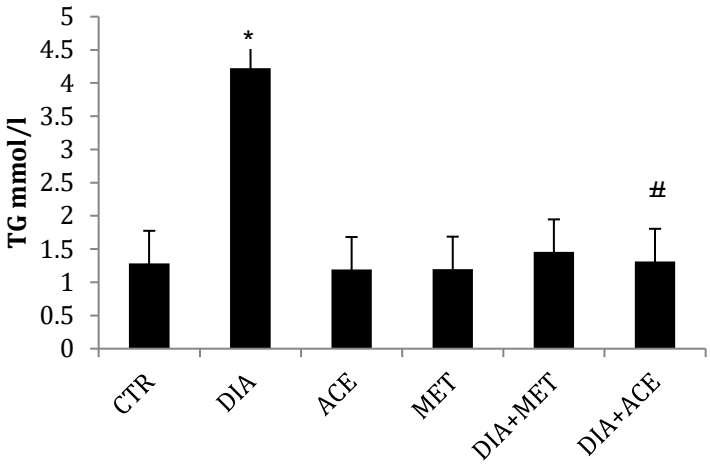
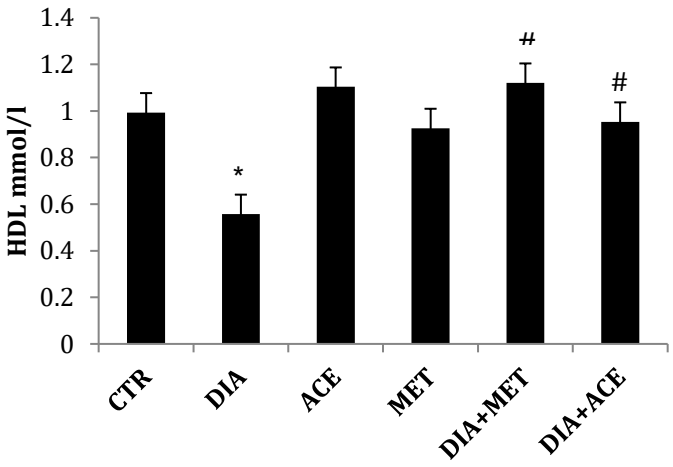


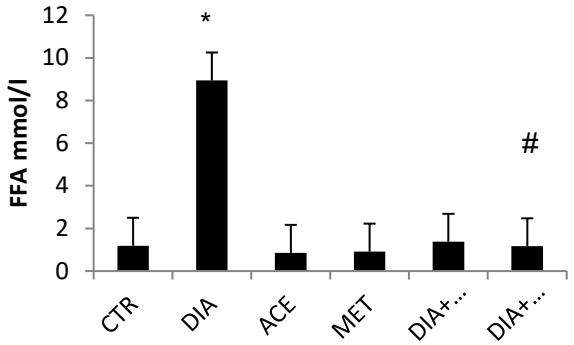
(c)



CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate

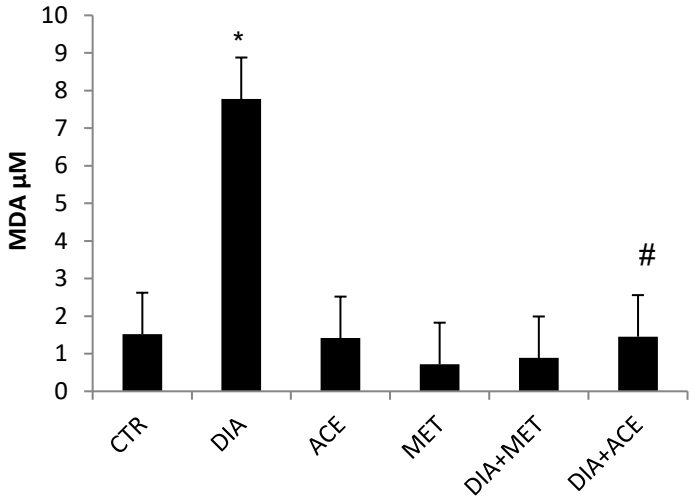
Figure 2: Effect of Acetate on (a) total cholesterol (TC), (b) triglyceride (TG), (c) High-density lipoprotein (HDL) in streptozoccin-induced diabetic rats. There was significant increase in TC and TG but decreased HDL of diabetic rats compared to the control whereas diabetic plus acetate treated rats showed significant decrease TC and TG but increase HDL. Data were analyzed by one-way ANOVA followed by Turkey's comparison *post hoc* test . Values are expressed as mean ± SEM of 5 rats per group. * DIA VS CTR $P<0.05$ # DIA+ACE VS DIA $P<0.05$

(a)

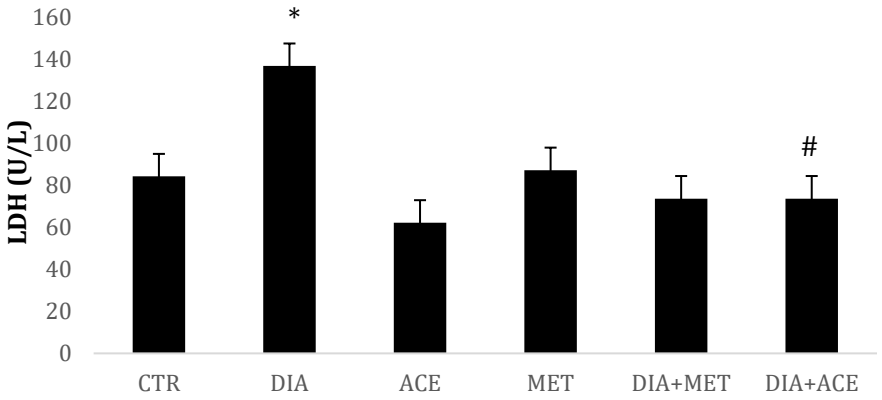


CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate

(b)

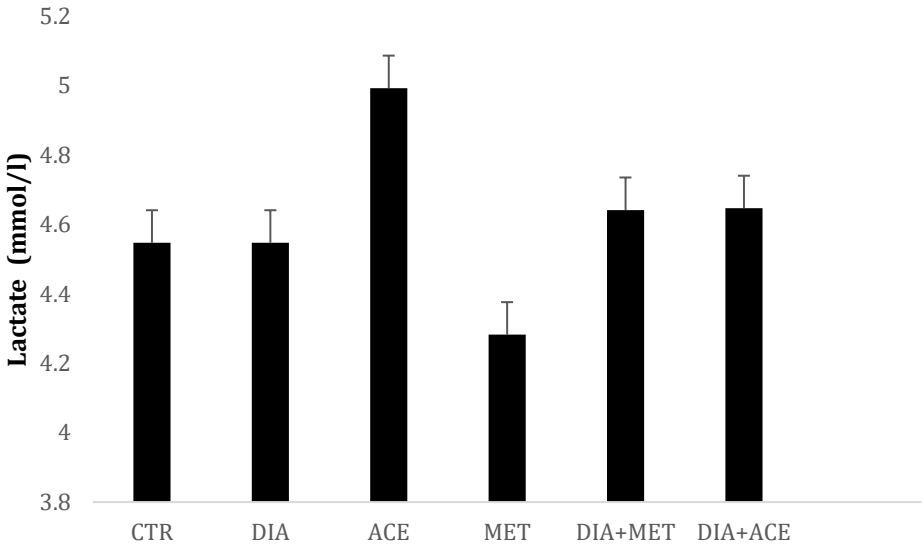


CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate

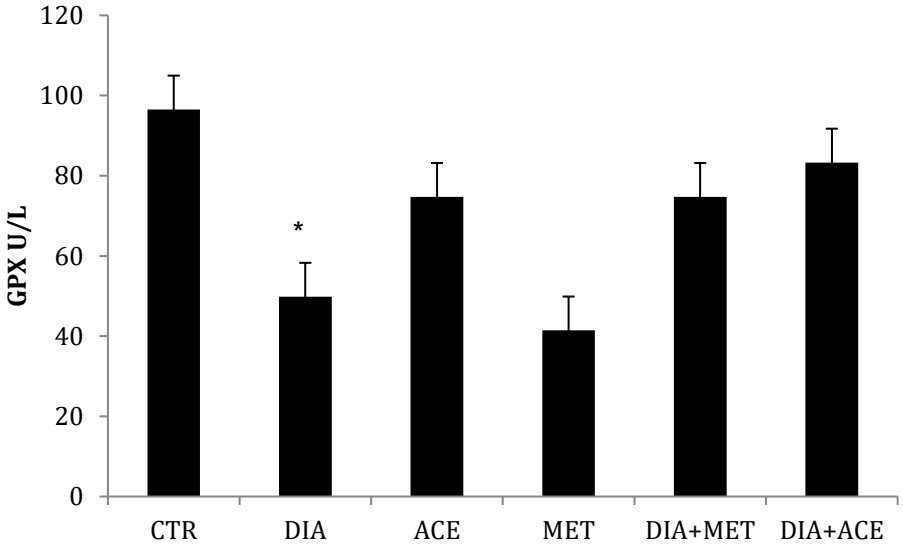


CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate

(d)

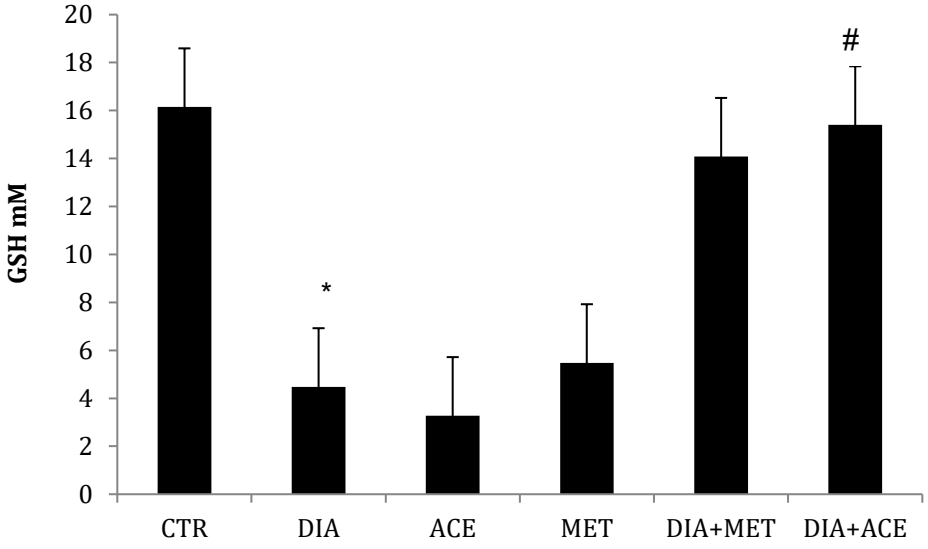


CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate



CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate

(f)



CTR=control, DIA= Diabetic untreated, ACE = Acetate, Met = metformin, Dia+Met= Diabetic treated with metformin, DIA+ACE = Diabetic treated with acetate

Figure 3: Effect of Acetate on (a) free fatty acid (FFA) (b) Malondialdehyde (MDA), (c) lactate (d) Lactate dehydrogenase (LDH), (e) Glutathione peroxidase (GPx) and (f) Glutathione (GSH) in streptozoccin-induced diabetic rats. There was significant increase in FFA, MDA and LDH but

decreased GPx and GSH of diabetic rats compared to the control whereas diabetic plus acetate treated rats showed significant decrease in FFA, MDA and LDH with increase in GPx and GSH. Data were analyzed by one-way ANOVA followed by Bonferroni *post hoc* test. Values are expressed as mean ± SEM of 5 rats per group. * DIA VS CTR $P<0.05$ # DIA+ACE VS DIA $P<0.05$

Discussion

The findings of this study demonstrate the beneficial effects of sodium acetate in improving key metabolic parameters and reducing oxidative stress in a rat model of diabetes mellitus. Sodium acetate administration significantly lowered fasting blood glucose, free fatty acids (FFA), and malondialdehyde (MDA) levels, while improving insulin sensitivity, lipid profiles, and antioxidant status as indicated by elevated glutathione (GSH) and glutathione peroxidase (GPx) levels. These results support the hypothesis that acetate exerts both metabolic and antioxidative benefits in diabetic conditions.

Glucose and insulin dysregulation, as shown in this study, are hallmark features of diabetes mellitus and are consistent with previous reports describing hyperglycemia and insulin resistance in experimental diabetes (Olaniyi et al., 2021). The observed reduction in fasting glucose and HOMA-IR following sodium acetate administration suggests improved insulin sensitivity. This aligns with evidence that short-chain fatty acids (SCFAs), such as acetate, enhance insulin signaling through the activation of G-protein-coupled receptors (GPCRs), particularly GPR41 and GPR43, which modulate glucose uptake and lipid metabolism (Tolhurst et al., 2012; Li et al., 2021; Archana et al., 2024).

Beyond glucose regulation, oxidative stress is a key contributor to the pathogenesis of diabetes. In this study, diabetic rats exhibited increased lipid peroxidation (MDA and FFA) and reduced antioxidant defenses (GSH, GPx), confirming the oxidative imbalance typical of diabetes (Valko et al., 2007; Evans et al., 2002). Sodium acetate treatment mitigated these effects, lowering MDA and enhancing GSH and GPx levels, indicating a restoration of redox homeostasis. Possible mechanisms include the activation of Nrf2 signaling, which upregulates antioxidant enzymes, improved mitochondrial function that limits reactive oxygen species (ROS) generation, and modulation of the gut microbiota, leading to reduced systemic inflammation (Zhao et al., 2019; Li et al., 2021). These pathways collectively explain acetate's capacity to attenuate oxidative stress and lipid peroxidation.

The present findings agree with earlier reports showing that acetate supplementation decreases oxidative stress and improves lipid metabolism. For example, Marques et al. (2016) and den Besten et al. (2015) demonstrated that acetate promotes fatty acid oxidation and reduces hepatic lipogenesis, resulting in improved lipid profiles and lower cardiovascular risk. Similarly, Zhao et al. (2019) reported that acetate reduces ROS generation and lipid peroxidation in diabetic mice. Therefore, our findings reinforce the growing consensus that acetate has multifaceted metabolic and antioxidant benefits.

However, this study has certain limitations. First, mechanistic biomarkers such as Nrf2, AMP-activated protein kinase (AMPK), and inflammatory cytokines were not assessed, which could have provided deeper insight into molecular pathways. Second, the absence of histopathological analysis limits conclusions about tissue-level protection.

Third, only male rats were used, which precludes evaluation of potential sex-specific differences. Future studies should investigate dose–response relationships, longer treatment durations, and combination therapy with standard antidiabetic drugs like metformin. Translational studies are also needed to evaluate the safety, efficacy, and pharmacodynamics of sodium acetate in human populations.

Conclusion

In conclusion, sodium acetate significantly ameliorated hyperglycemia, dyslipidemia, and oxidative stress in streptozotocin-induced diabetic rats. These effects appear to involve mechanisms related to GPCR activation, Nrf2 signaling, mitochondrial protection, and gut microbiota modulation. The findings suggest that sodium acetate holds therapeutic potential as an adjunct strategy for managing diabetes and preventing its oxidative and cardiovascular complications. Further mechanistic and translational research is needed to validate these outcomes in clinical settings.

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