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Hypolipidemic effect of N-acetylcysteine against dexamethasone-induced hyperlipidemia in rats

S. B. Mada[1], M. M. Abarshi[1], A. Garba[1], K. L. Sharehu[1], O. P. Elaigwu[1], M. J. Umar[1], B. Musa[1], H. A. Mohammed[1], I. Garba[2]

[1]Department of Biochemistry, Ahmadu Bello University, Zaria, [2]Department of Medical Microbiology, Usmanu Danfodiyo University Sokoto, Sokoto, Nigeria.

***Corresponding author:**
S. B. Mada,
Department of Biochemistry,
Ahmadu Bello University,
Zaria, Nigeria.

sbmada@abu.edu.ng

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ABSTRACT

Objective: The liver is a key metabolic organ involved in lipid metabolism and maintenance of cholesterol homeostasis in the body. However, hypercholesterolemia and oxidative stress is associated with the fatty liver which is the major risk factor associated with cardiovascular diseases (CVDs). The objective of this study was to investigate the hypolipidemic property of N-acetylcysteine (NAC) in dexamethasone-induced hyperlipidemic rats.

Materials and Methods: Dexamethasone (10 mg/kg) was administered on alternate days intraperitoneally for 28 days to induce hyperlipidemia. NAC (50 mg/kg and 100 mg/kg) was daily administered intraperitoneally for 28 days. After 24 h of the last treatment blood and liver samples were collected.

Results: The relative body and liver weights, activities of serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lipid profile, and antioxidant defense markers were measured. The result indicated that the treatment of hyperlipidemic rats with 50 and 100 mg/kg NAC significantly ($P < 0.05$) prevented dexamethasone-induced body weight loss and restored liver weight. In addition, NAC reduced the elevation of hepatic enzymes activities induced by dexamethasone. Moreover, NAC exhibits hypolipidemic effect as demonstrated by reversal of serum levels of total cholesterol, triacylglycerol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and atherogenic index.

Conclusion: These findings indicated that NAC was able to restore dyslipidemia induced by dexamethasone through improving liver function parameters and augments antioxidant defense systems. Altogether the anti-hyperlipidemic effects exhibited by NAC might have been mediated partly through antioxidant actions and could be beneficial against CVDs.

Keywords: Dexamethasone, Oxidative stress, Hyperlipidemia, N-acetylcysteine, Antihyperlipidemic effect

INTRODUCTION

The liver is a key metabolic organ responsible for lipid metabolism and maintenance of cholesterol homeostasis in the body. Although, cholesterol is an essential constituent of biomembranes and acts as a precursor for the synthesis of bile acids, hormones, and vitamins,[1] increase in the blood level of cholesterol and oxidative stress is associated with fatty liver and thus represents the major risk factor for development or progression of atherosclerosis and cardiovascular diseases (CVDs).[2-6] CVDs have been described as one of the major causes of morbidity and mortality in the world. Worldwide more than 12 million people die from CVDs every year[7] and this will be on the rise and become the world leading cause of death and disability by the year 2020.[8] In addition, CVDs exhibit complex interplays or synergistic actions between oxidative stress

and inflammatory processes.[9-11] Humans are constantly exposed to free radicals resulting from several factors.[12] The excessive free radical production may induce a number of alterations on cell constituents, leading to inactivation of enzymes, production of reactive oxygen species (ROS), oxidative damage to nucleic acids, proteins, and peroxidation of membrane lipids.[13] Thus, liver is prone to damage by ROS owing to the fundamental role it plays in the maintenance of systemic lipid homeostasis.[14] Several studies have demonstrated that hyperlipidemia reduces the hepatic antioxidant defense system,[15,16] increases lipid peroxidation, and alters enzymatic and non-enzymatic antioxidant status in rats fed a high cholesterol diet for 30 days.[16] Previous studies have demonstrated that antioxidant enzymes such as superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase can synergistically neutralize oxidative damage produced by free radicals.[12,17] The primary risk factors associated with hyperlipidemia or progression of atherosclerosis is elevated blood levels of total cholesterol (TC), triacylglycerol (TAG), low-density lipoprotein cholesterol (LDL-c), and very LDL-c (VLDL-c).[18] Even though most of the conventional lipid-lowering drugs such as fibrates, statins and sequestrants could regulate lipid metabolism by different mechanisms, they exhibit adverse effects such as hyperuricemia, diarrhea, nausea, severe muscle damage (myopathy), gastric irritation, flushing, dry skin, abnormal liver function, and other contraindications which have masked their popularity.[19] Hence, in the past decade interest in nutraceuticals and functional foods has inspired the search for new effective cholesterol-lowering agents from food sources.[20]

N-acetylcysteine (NAC) is a hydrophilic cysteine-containing compound naturally produced by allium plants such as garlic and onion. NAC exhibits direct and indirect antioxidant activity due to its sulfhydryl group and is a precursor for reduced GSH.[21] GSH is the most abundant intracellular antioxidant compound.[22,23] It scavenges free radicals, provides reducing equivalents for the activity of GSH-peroxidase, a powerful defense against peroxides.[24] Previous study demonstrated that NAC increases GSH level, decreases tissue damage, reduced oxidative damage, and lipid peroxidation.[25] In addition, NAC protects the liver against high fat-induced oxidative damage and effectively decreases saturated fat-induced TAG and cholesterol accumulation in mice liver.[26] Therefore, the present study was undertaken to investigate anti-hyperlipidemic and antioxidant effects of NAC against dexamethasone-induced hyperlipidemia in rats.

MATERIALS AND METHODS

Chemicals

NAC and dexamethasone sodium phosphate [Figure 1a and b] with purity >98% were purchased from Sigma-Aldrich Chemical Co., St. Louise, Missouri, USA. Biochemical diagnostic kits were purchased from Randox Ltd., Co. UK. All other kits and reagents used in the present study were of analytical grade.

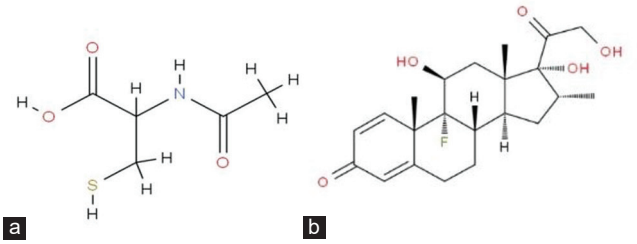

Figure 1: Structures of N-acetylcysteine (NAC) and dexamethasone. (a) NAC, (b) dexamethasone. Source from National Center for Biotechnology Information. PubChem Compound Database; CID = 5743, https://pubchem.ncbi.nlm.nih.gov/compound/5743.

Animals

Twenty-eight (three months old) female Wister rats weighing between 140 and 150 g were obtained from Small Animal Unit, Department of Veterinary Pharmacology and Toxicology, Ahmadu Bello University, Zaria. The animals were kept in stainless still cages on a 12 h light/dark cycle at room temperature with free access to water and normal rats feed *ad libitum*. This research was approved by the Institutional Animal Ethical Committee of Ahmadu Bello University, Zaria before the commencement of the study. Furthermore, the animals were treated in line with the National Institute of Health guidelines for the care and use of animals.

Experimental design and induction of hyperlipidemia

The hyperlipidemia was induced in experimental rats by intraperitoneal injection of dexamethasone (10 mg/kg) 3 times a week and continued up to 4 weeks as described previously.[27] Before the commencement of trials with NAC, few animals from the induced pool were selected and sacrificed. The levels of lipid profile were assessed, relative to control non-induced animals, to confirmed induction of hyperlipidemia. Thereafter, animals were divided into four groups of six each. Group I received vehicle and served as normal control rats; Group II received an intraperitoneal injection of 10 mg/kg dexamethasone 3 times a week up to 4 weeks and served as hyperlipidemic control. Group III-IV received an intraperitoneal injection of 10 mg/kg dexamethasone 3 times a week up to 4 weeks and were simultaneously treated intraperitoneally with 50 mg/kg and 100 mg/kg of NAC, respectively, for 4 weeks. After 4 weeks of treatment, rats were fasted overnight and under mild anesthesia, blood samples were taken through cardiac puncture. The animals were euthanized and liver tissues were collected.

Blood samples were allowed to clot and centrifuged at 3000× g for 10 min and the serum obtained was used for biochemical analysis.

Measurement body and liver weight

The body weight of the experimental animals was measured weekly throughout the 4 weeks period of the study. The weight of liver tissue from each rat was measured immediately after sacrificed using the electronic weighing balance.

Lipid profile assays

TC, TAG, LDL-c, and high-density lipoprotein cholesterol (HDL-c) levels were estimated using assay kits (Randox Ltd., Co. UK) according to the manufacturer's instructions. Atherogenic index (AI) was determined as described previously[28] using the following formula: AI = (TC-HDL-c)/HDL-c.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) assays

The serum activities of AST and ALT were assayed spectrophotometrically using assay kits (Randox Ltd., Co. UK) based on the method of Reitman and Frankel.[29] ALP was also assayed spectrophotometrically using assay kits (Randox Ltd., Co. UK) based on the previously described method.[30]

SOD and CAT activities assays

SOD activity was assayed as previously described.[31] The reaction mixture contained 200 µl sample and 200 µl pyrogallol (2 mM) and the volume was made up to 3 ml with diethylenetriamine penta-acetic acid (50 mM-Tris–HCl buffer 1 mM, pH 7.4). The inhibition of pyrogallol auto-oxidation by SOD present in the sample was measured by monitoring the increase in absorbance at 420 nm for 1 min using Specord 200 double-beam ultraviolet (UV)/visible spectrophotometer (Analytik Jena, Germany). The amount of enzyme that inhibited the auto-oxidation of pyrogallol by 50% was defined as one unit. The enzyme activity was expressed in units/mg of protein. CAT activity was assayed as previously described.[32] Briefly, the reaction mixture contained 200 µl samples, 300 µl H_2O_2 (30 mM), and volume was made up to 3 ml with phosphate buffer (50 mM, pH 7.4). The reaction was initiated by the addition of H_2O_2 and the decomposition of H_2O_2 by CAT was monitored using Specord 200 double-beam UV/visible spectrophotometer (Analytik Jena, Germany) by following the decrease in absorbance at 240 nm for 1 min. The enzyme activity was expressed in units/mg of protein. One unit of enzyme activity is defined as 1 µmol of H_2O_2 consumed per minute.

Measurement of GSH and malondialdehyde (MDA) level

The level of MDA in serum samples was measured using the method of Uchiyama and Mihara.[33] The binding of thiobarbituric acid to MDA, which was formed during lipid peroxidation, results in a chromogenic complex. Change in absorption was measured spectrophotometrically at 532 nm. The obtained MDA level was normalized by total protein content. The serum GSH concentration was determined by the reaction of GSH with 5, 5'-dithiobis-2-nitrobenzoic acid to produce a colored product that could be measured spectrophotometrically at 412 nm.[34] GSH level from each sample was normalized by total protein content.

Statistical analysis

Data (mean ± standard error of the mean, n = 6) were analyzed using GraphPad Prism 5.01 version (GraphPad Statistical Software Inc., San Diego, CA, USA). Comparisons between the groups were made using one-way analysis of variance and Turkey's *post hoc* test was employed to test the significance of the difference between the groups, and $P < 0.05$ was considered as statistically significant.

RESULTS

Effect of NAC on body weight of dexamethasone-induced hyperlipidemic rats

At the beginning of the study, there was no significant ($P > 0.05$) difference in the body weight for all the experimental rats. However, intraperitoneal injection of dexamethasone to rats on alternate days for 4 weeks resulted in significant ($P < 0.05$) reduction in body weight compared to untreated control rats [Table 1]. Interestingly, daily

Table 1: Effect of NAC on body weight of dexamethasone-induced hyperlipidemic in rats.

Group	Week 0	Week 1	Week 2	Week 3	Week 4
Control	140.70±3.98^{a}	145.30±4.36^{a}	153.13±4.33^{a}	162.26±3.90^{a}	175.33±4.74^{a}
Dexa (10 mg/kg)	139.90±4.79^{a}	135.30±3.59^{b}	125.17±3.66^{b}	117.30±2.56^{b}	112.51±2.59^{b}
Dexa+NAC (50 mg/kg)	140.44±3.33^{a}	138.70±2.57^{b}	136.80±4.89^{c}	140.70±5.71^{c}	143.22±3.02^{b}
Dexa+NAC (100 mg/kg)	141.32±3.65^{a}	137.50±3.19^{b}	139.70±7.56^{cd}	142.20±3.32^{cd}	145.68±2.82^{d}

Values are expressed as mean±SEM (n=6). Values with different superscript letters are significantly different at P<0.05. SEM: Standard error of the mean, NAC: N-acetylcysteine

treatment with 50 and 100 mg/kg NAC for 4 weeks was able to significantly ($P < 0.05$) prevent dexamethasone-induced body weight loss when compared to the group treated with dexamethasone alone [Table 1].

Effect of NAC on liver weight in hyperlipidemic rats

Treatment with dexamethasone-induced significant ($P < 0.05$) increases in liver weight in comparison to untreated control rats. However, the increase in liver weight was reversed by treatment with 100 mg/kg NAC but there was no significant ($P > 0.05$) difference between group treated with 50 mg/kg NAC and the group treated with dexamethasone alone [Figure 2a]. These data suggest the beneficial effect of NAC against dexamethasone-induced fatty liver.

Effect of NAC on some hepatic enzymes in hyperlipidemic rats

The activities of some hepato-specific enzymes, namely, ALT, AST, and ALP were significantly increased ($P < 0.05$) in dexamethasone-treated rats compared to control [Figure 2b-d]. However, daily treatment with 50 and 100 mg/kg NAC for 4 weeks significantly ($P < 0.05$) reduced the activities of these hepatic enzymes when compared to the group treated with dexamethasone alone [Figure 2b-d].

Effect of NAC on serum lipid profile in hyperlipidemic rats

Dexamethasone administration-induced hyperlipidemia in rats as revealed by significant ($P < 0.05$) increase in TC, TAG, LDL-c, AI, and significant ($P < 0.05$) reduction in HDL-c level [Figure 3a-e]. Interestingly, the treatment of hyperlipidemic

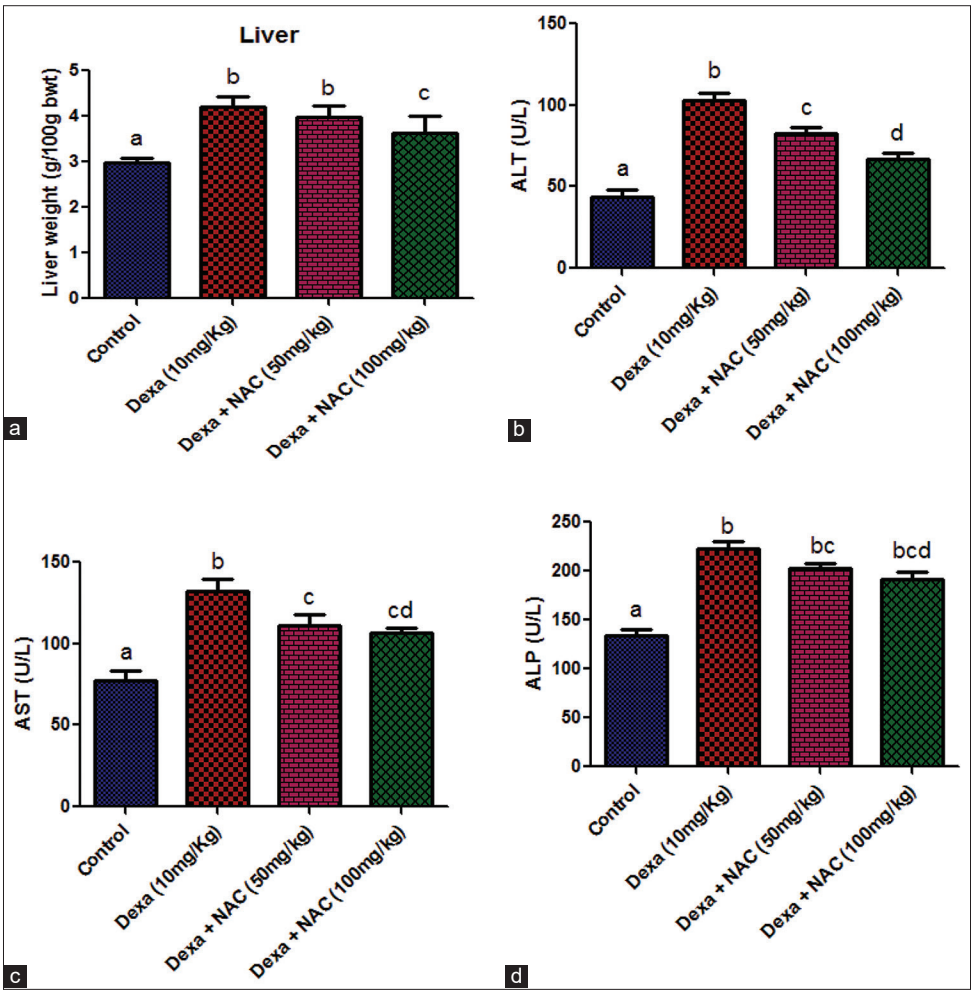

Figure 2: Effect of N-acetylcysteine on liver weight and the hepatic enzymes activities in dexamethasone-induced hyperlipidemic rats. (a) Liver weight (g/100 g), (b) alanine aminotransferase activity (U/L), (c) aspartate aminotransferase activity (U/L), (d) alkaline phosphatase activity (U/L). Mean values are expressed as mean ± standard error of the mean ($n = 6$). A column with different superscript letters is significantly different at $P < 0.05$.

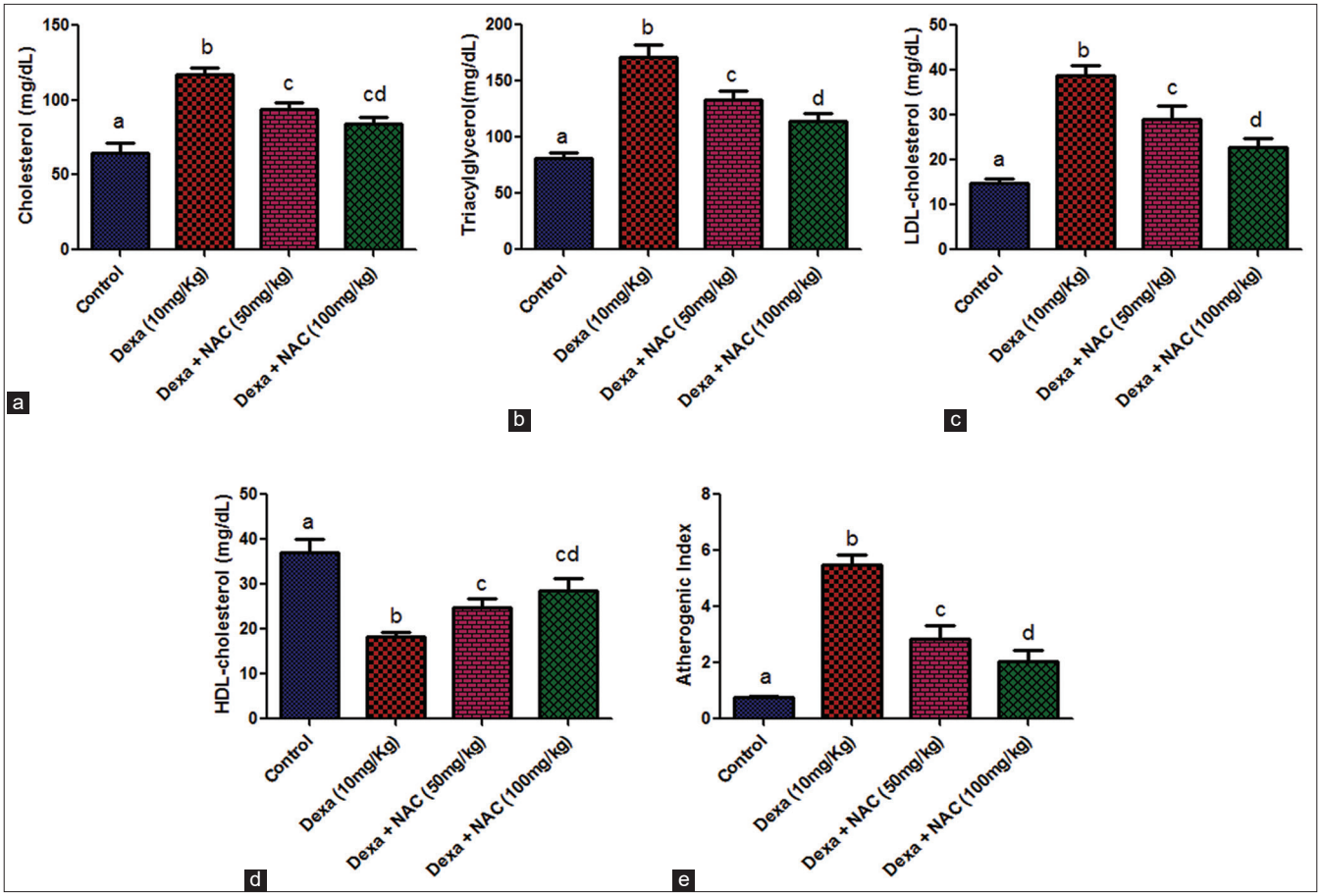

Figure 3: Effect of N-acetylcysteine on lipid profile and atherogenic index (AI) in dexamethasone-induced hyperlipidemic rats (a) cholesterol (mg/dlL), (b) triacylglycerol (mg/dL), (c) low-density lipoprotein cholesterol (mg/dL), (d) high-density lipoprotein cholesterol (mg/dL), (e) AI. Mean values are expressed as mean ± standard error of the mean (n = 6). Column with different superscript letters are significantly different at $P < 0.05$.

rats with NAC for 4 weeks significantly ($P < 0.05$) decreased dexamethasone-induced elevation of serum lipid profile in a dose-dependent manner when compared to the untreated group [Figure 3a-e].

Effect of NAC on antioxidant enzymes activity in hyperlipidemic rats

The serum SOD and CAT activities were significantly ($P < 0.05$) increased following dexamethasone injection in comparison to control [Figure 4a and b]. However, the administration of NAC significantly ($P < 0.05$) prevented the decrease of SOD and CAT activities compromised by dexamethasone when compared to the untreated group [Figure 4a and b].

Effect of NAC on oxidative stress markers in hyperlipidemic rats

Dexamethasone-induced increases of oxidative stress markers. As expected, there was significant ($P < 0.05$) increased in serum MDA level and decrease in serum GSH level when compared to control [Figure 4c and d]. However, the administration of NAC significantly ($P < 0.05$) reversed the alteration in these oxidative stress biomarkers induced by dexamethasone [Figure 4c and d].

DISCUSSION

The adverse effect of prolonged treatment of dexamethasone includes the induction of insulin resistance, and metabolic disorders such as hyperleptinemia, loss of appetite, and weight loss.[35,36] We have demonstrated that dexamethasone treatment caused a significant decrease in body weight and elevates liver weight. The present data are consistent with the previous study.[37] Furthermore, it is of interest to note that NAC treatment reversed the weight loss induced by dexamethasone to some extent. The improvement of body weight by NAC may be linked to the increase in sensitivity to insulin and glucose utilization.[38] The liver actively detoxifies endogenous and exogenous chemicals, making it vulnerable

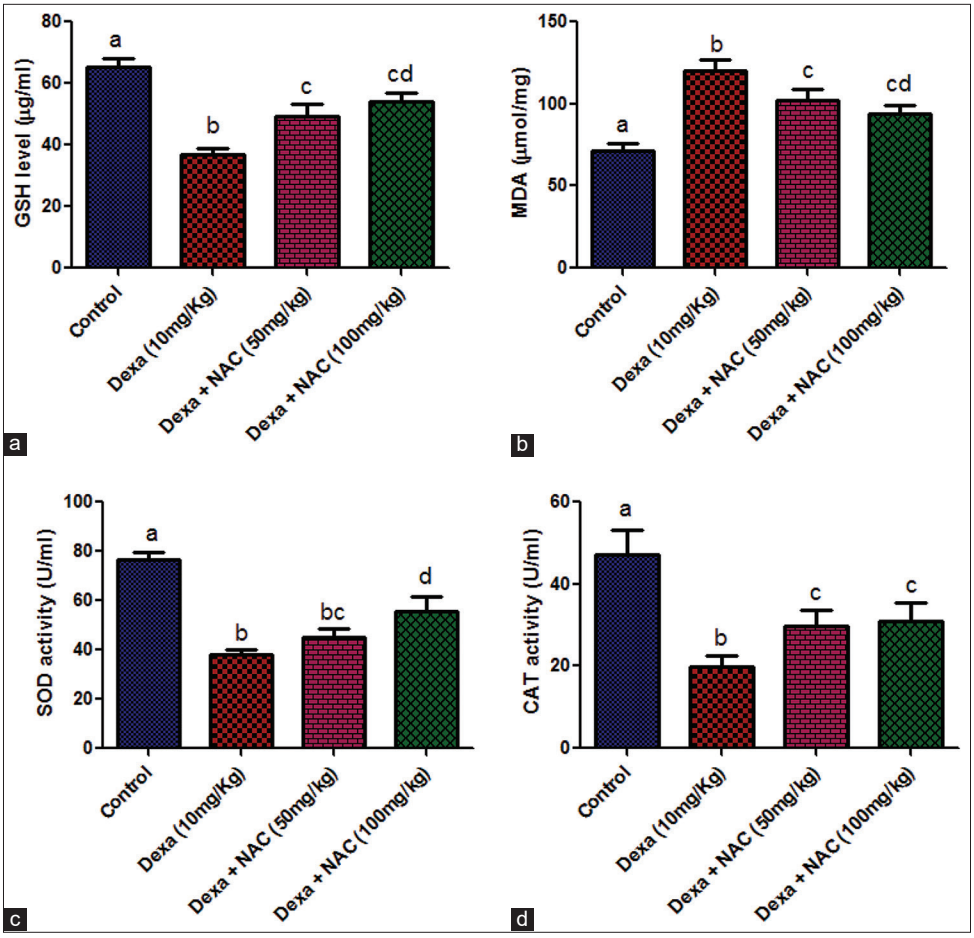

Figure 4: Effect of N-acetylcysteine on antioxidant defense system in dexamethasone-induced hyperlipidemic rats. (a) glutathione level (µg/ml), (b) malondialdehyde (µmol/mg), (c) superoxide dismutase activity (U/ml), (d) catalase activity (U/ml). Mean values are expressed as mean ± standard error of the mean ($n = 6$). Column with different superscript letters is significantly different at $P < 0.05$.

to injury and dysfunction. In addition, injury to liver tissue due to hyperlipidemia alters its transport function and membrane permeability, leading to elevation and leakage of AST, ALT and ALP from the cells which reflect severe hepatic damage.[39,40] The results of this study suggest that NAC prevented the elevation of AST, ALT, and ALP activities. This protective action of NAC could be due to a reduction of lipid peroxidation and enhancement of antioxidant activity in the liver. Our result is consistent with the previous study which reported that bioactive constituents of *Ricinodendron heudelotii* leaf extract ameliorated artemisinin-induced oxidative stress and hepatic dysfunction in male Wistar rats.[41] Moreover, dexamethasone induces elevation of serum lipid profile and consequently may lead to the accumulation of lipids in the liver. The stimulation of the TAG production could lead to increased secretion of VLDL-c which causes an imbalance in lipid metabolism leading to hyperlipidemia.[42,43] Thus, an animal models of dexamethasone-induced hyperlipidemic rats have been successfully used for the evaluation of lipid-lowering property of antioxidant compounds.[36] HDL-c transports cholesterol from peripheral tissues to the liver for catabolism causing significant reduction in TC, TAG, and VLDL-c. The increased HDL-c facilitates the transport of TAG or cholesterol from serum to liver through reverse cholesterol transport, where it is catabolized and excreted.[44] Earlier study reported that probiotic *Lactobacillus fermentum* MTCC: 5898-fermented milk reduces the markers of hyperlipidemia, oxidative stress, and inflammatory response in rats fed with cholesterol-enriched diet.[45] Our result demonstrated that NAC administration lowered serum cholesterol, TAG, LDL-c level, reduced AI, and elevated serum HDL-c level in hyperlipidemic rats. The hypolipidemic effects of NAC against dexamethasone suggest its ability to regulate cholesterol biosynthesis and reverse hyperlipidemia by the restoration of cholesterol homeostasis, possibly through an increase in excretion of TAG through feces or by inhibiting the action of hepatic TAG-lipase on HDL-c which might contribute to rapid catabolism of lipids through extra-hepatic tissues.[46] Similarly, the present data were consistent with earlier reports that chrysin; a flavonoid (10 mg/kg) exhibited antihyperlipidemic

effect by lowering plasma TC, non-HDL cholesterol, and TAG levels in triton WR-1339-induced hyperlipidemia in mice.[47] Moreover, the influence of oxidative stress in the progression and pathogenesis of degenerative diseases is well documented and it is well-known that lipid peroxidation increases when free radical production overwhelms the total antioxidant defense system.[48] Oxidative stress has been linked with oxidative modification of biomolecules which is believed to be the origin of many diseases including atherosclerosis.[49] Oxidative stress has been shown to coexist with a decrease in GSH level, increase in lipid peroxidation and impairment in the activities of endogenous antioxidant enzymes such as CAT and SOD.[50] Thus, antioxidants constitute one of the major targets of many anti-atherogenic agents preventing atherosclerosis and related coronary artery disorder, inflammation, and CVDs.[51] Another study reported that treatment with atorvastatin may not only reduce free radical production but also enhances GSH contents, increase SOD activity and lowers MDA levels in myocardial tissue in a diabetic rat model.[52] In the present study, we established that NAC reversed the alteration of oxidative stress markers induced by dexamethasone as reflected by an increase in GSH level, decrease MDA level, and upregulated SOD and CAT activities in hyperlipidemic rats. Interestingly, we have demonstrated that treatment with NAC enhances the capacity of antioxidant defense systems to protect the liver from oxidative stress induced by dexamethasone. This result once again highlights the antioxidant action of NAC and it is quite reasonable to suggest that the possible mechanism of hypolipidemic effects exhibited by NAC might have been mediated through antioxidant activities and could be beneficial against CVDs.

CONCLUSION

Treatment of hyperlipidemic rats with NAC restored liver biomarker enzymes and augments antioxidant defense system. Altogether the anti-hyperlipidemic effects exhibited by NAC might have been mediated partly through antioxidant actions and could be beneficial against CVDs. However, further studies are needed to explore detail molecular mechanisms on how NAC alleviates dexamethasone-induced alterations in liver tissue and hyperlipidemia in rats.

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Declaration of patient consent

Declaration of patient consent is not applicable for this study. However, prior ethical approval was obtained from the Institutional Animal Ethical Committee of Ahmadu Bello University, Zaria before commencement of the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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