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AMELIORATIVE EFFECT OF N-ACETYL-L-CYSTEINE ON SODIUM DICHROMATE-INDUCED ALTERATIONS OF HAEMATO-BIOCHEMICAL PARAMETERS IN RATS

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ABSTRACTS

Protective effect of antioxidant N-acetyl-L-cysteine (NAC) on sodium dichromate induced-haemato-biochemical alterations was study. Rats were divided into four treatment groups of ten rats each. Group 1 received DMSO (2 mL/ kg) and served as normal control. Group 2 were administered with sodium dichromate (10 mg/kg) in 0.2 mL deionized water and served as negative control. Group 3 and 4 were administered with sodium dichromate (10 mg/kg) in 0.2 mL deionized water each and NAC (25 and 50 mg/kg) in 0.2 mL DMSO respectively. The treatment was carried out daily for 12 weeks. Results revealed NAC administration significantly ($P < 0.05$) reversed the hepatic damage in a dose-dependent manner when compared to non-treated group. Interestingly, our results showed administration of NAC significantly ($P < 0.05$) increase SOD and CAT activities along with elevation of GSH and decrease MDA levels in dose-dependent manner when compared to non-treated group. Moreover, NAC administration reversed the increase in urea and creatinine levels and restored haematological parameters when compared to non-treated group. The present study, suggests that NAC possess protective effect against sodium dichromate induced-alterations of haemato-biochemical parameters in rats.

KEYWORDS: Sodium dichromate; N-acetyl-L-cysteine; oxidative damage; haematological parameter

1. INTRODUCTION

Exposure to heavy metals is still on the increase in some parts of the world, particularly in developing countries. Chromium (Cr), a naturally occurring heavy metal, exists in many

oxidation states, but the trivalent Cr (III) and hexavalent Cr (VI) forms are the most biologically active oxidation states and common in the environment.[1] The trivalent Cr (III) is an essential trace element required by humans and animals.[2] It improves the action of insulin by enhancing its binding to receptor for effective utilization of carbohydrates, lipids and proteins.[3] One of the soluble hexavalent salts of chromium Cr (VI) is sodium dichromate, which is the most prevalent in the environment mostly through industrial emission and is widely recognized as genotoxic, allergen, carcinogen, mutagen, and teratogen toward humans and animals.[4, 5] The wide distribution of sodium dichromate in the environment occurs due to its extensive exploitation to produce stainless steel, alloy cast irons, chrome, and wood treatment products, dry battery, tanning of leather or pigments.[6, 7] The fate of chromium in the environment is largely dependent on its oxidation state. For instance, the reduction of Cr (VI) to Cr (III) results in the formation of reactive oxygen species (ROS) leading to oxidative tissue damage and cellular injury. Acute and chronic toxicity in both animals and humans are mainly caused by Cr (VI) compounds.[8] Oxidative stress occurs due to the imbalance between reactive oxygen species (ROS) and activity of the antioxidant systems. These ROS can damage proteins, lipids and DNA, altering the organism's structure and functions which could lead to a broad spectrum of diseases.[9] N-acetyl-L-cysteine (NAC) a sulfhydryl substance is a derivative of amino acid L-cysteine commonly used as a mucolytic agent, antidote due to acetaminophen intoxication and as prophylaxis against renal injury.[10, 11, 12] Also, NAC demonstrated anti-inflammatory effect by inhibition of many proinflammatory cytokines activities including TNF-α, IL-6, IL-8.[13] Presently, NAC is known mainly as an antioxidant displaying direct and indirect activities, scavenge reactive oxygen species (ROS) such as superoxide radical (O_2), hydrogen peroxide (H_2O_2) and hydroxyl radical OH.[14] The antioxidant function of NAC increases the intracellular levels of glutathione, combat oxidative stress induced damage in various tissues[15, 16] and could at least in part, enhance immunity by maintaining the functional and structural integrity of important immune cells.[17] Despite remarkable information regarding the toxic and deleterious effects of Cr (VI) in both humans and animals. Thus, to the best of our knowledge, no study is conducted to investigate the protective effect of NAC on chromium-induced haematological and biochemical alterations in rats. The aim of the present study was to determine whether NAC has protective effects on sodium dichromate-induced haematological and biochemical alteration in rats.

2. MATERIALS AND METHODS

2.1. Chemicals

N-acetyl-L-cysteine (NAC) > 98% purity was purchased from Sigma Chemical Co (St. Louis, MO, USA). Sodium dichromate and dimethylsulfoxide (DMSO) were purchased from Merck India Ltd (Mumbai, India). Biochemical diagnostic kits were purchased from Randox Ltd., Co. (UK). All other chemicals and reagents were of analytical grade obtained from local firms.

2.2. Experimental Animals

Male Wister albino rats of two month old weighing between 140-160g were purchased from Animal house, Department of Pharmacology, Ahmadu Bello University Zaria, Nigeria and were used throughout the experiments. The animals were kept in a clean plastic cage under 12 hrs light/dark cycles at temperature of 25±3.0ºC. All animals were allowed free access of water and standard pellet diets *ad libitum* and allowed to acclimatize to the laboratory environment for one week before the commencement of the experiment.

2.3. Experimental design and Animal treatment

Forty apparently healthy male Wister rats were used in the present experiment. The animals were randomly divided into four groups of 10 rats per group. Group 1 was orally administered with 2 mL/ kg body weight vehicle (DMSO), served as normal control. Group 2 were administered with only 10 mg/kg body weight sodium dichromate in 0.2 mL deionized water, served as negative control. Group 3 and 4 were orally administered with 10 mg/kg body weight sodium dichromate in 0.2 mL deionized water each and then orally treated with 25 and 50 mg/kg body weight NAC respectively in 0.2 mL DMSO. The treatment was carried out daily throughout the 12 weeks of the experimental period. After the last day of treatment, the animals were fasted overnight and anaesthetized by intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood sample was collected through cardiac puncture and divided into plain and EDTA-containing centrifuge tubes and centrifuged at 2000 rpm for 5 min at 4ºC for obtaining serum and plasma respectively.

2.4. Tissue preparation

Liver was dissected out, weighed and washed using chilled phosphate buffered saline (PBS). Tissue was minced and homogenized (10% w/v) in PBS (pH7.4) and centrifuged (3000g for 10 min). The resulting clear supernatant was used for various enzymatic and non-enzymatic biochemical assays. This study was approved by the Local Animal Ethics Committee of the

Ahmadu Bello University Zaria, Nigeria. The animals were treated in accordance with its guidelines and regulations.

2.5. Body weight measurement

The body weights of rats were measured before the commencement of the experiment, thereafter weekly up to the last week of the study period.

2.6. Estimation of haematological parameters

The blood plasma of haematological parameters; red blood cells (RBCs), packed cell volume (PCV), haemoglobin (Hb) and white blood cells (WBCs) were measured using auto haematogy analyser (Merck specialities Pvt. Ltd).

2.7. Estimation of liver markers

The blood serum activities of alanine transaminase (ALT) aspartate transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (TBL) were assayed spectrophotometerically using diagnostic kits Randox Ltd., Co. (UK), according to the manufacturer's instructions.

2.8. Estimation of kidney function biomarkers

The blood serum level of urea and creatinine were assayed using diagnostic kits purchased from Randox Ltd., Co. (UK), according to manufacturer's instructions.

2.9. Estimation antioxidant and lipid peroxidation biomarkers in liver

The concentration of reduced glutathione (GSH) in liver tissue was measured based on 5, 5'-dithio-bis-[2-nitrobenzoic acid] (DTNB) according to the method described by Ellman.[18] Catalase (CAT) activity in liver tissue was determined spectrophotometerically, according to the method of Aebi,[19] by measuring the decrease in absorbance of H_2O_2 at 240 nm using specord 200 double beams UV/visible spectrophotometer. Superoxide dismutase (SOD) activity in liver tissue was estimated spectrophotometerically using specord 200 double beams UV/vsible spectrophotometer based on the inhibition of pyragallol auto-oxidation according to the method described by Marklund and Marklund.[20] The concentration of malondialdehyde (MDA) in liver tissue was estimated based on thiobarbituric acid reaction substances (TBARS) using the method described by Uchiyama and Mihara.[21] Protein concentration in liver was assayed by the method of Lowry *et al.*[22] using bovine serum albumin as a standard.

2.10. Statistical Analysis

Data was analysed and presented as mean ± standard deviation using GraphPad Prism 5.01 version. Comparisons between values were made using one-way analysis of variance (ANOVA). Turkey's Post hoc test was employed to test the significance of difference between the groups and $P < 0.05$ was considered as statistical significant.

3. RESULTS

3.1. Body weight changes

We evaluated the body weight changes of the animals before and at the end of 12 weeks of the study (initial and final body weight). The result indicated a significant ($P < 0.05$) decrease in the body weight of the rats in sodium dichromate (10 mg/kg) treated group in comparison to control group (Table 1). Interestingly, co-administration of sodium dichromate with NAC (25–50 mg/kg) significantly ($P < 0.05$) alleviates the loss of body weight in a dose-dependent manner compared to sodium dichromate group.

Table 1: Protective effect of NAC administration against sodium dichromate-induced body weight loss in rats

Body weight (g)	Group 1	Group 2	Group 3	Group 4
Initial	147.40 ± 3.77^{a}	$154.5.0 \pm 2.95^{a}$	156.90 ± 2.50^{a}	157.40 ± 2.59^{a}
Final	160.60 ± 2.73^{b}	140.90 ± 4.80^{b}	164.60 ± 2.82^{b}	168.40 ± 1.64^{b}

Values are Mean ± SD (n=10). Values with different superscripts down the column are statistically different at $P < 0.05$.

3.2. Effects of NAC administration on the biomarkers of liver function in rat exposed to sodium dichromate

Oral administration of sodium dichromate (10 mg/Kg) caused abnormal liver function in treated rats when compared to control group (Fig. 1). The activities of hepatospecific enzymes in liver tissue such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and the level of total bilirubin (TB) were significantly increased ($P < 0.05$) whereas the level of total protein significantly ($P < 0.05$) decrease in sodium dichromate treated rats in comparison with control rats. Interestingly, co-administration of sodium dichromate along with NAC (25–50 mg/kg) significantly ($P < 0.05$) reverse the situation when compared to rats group treated with sodium dichromate alone. Restoration of hepatic biomarker enzymes, total bilirubin and

total protein were more at higher dose level (50 mg/kg) of NAC than the lower dose (25mg/kg) when compared with sodium dichromate treated rats.

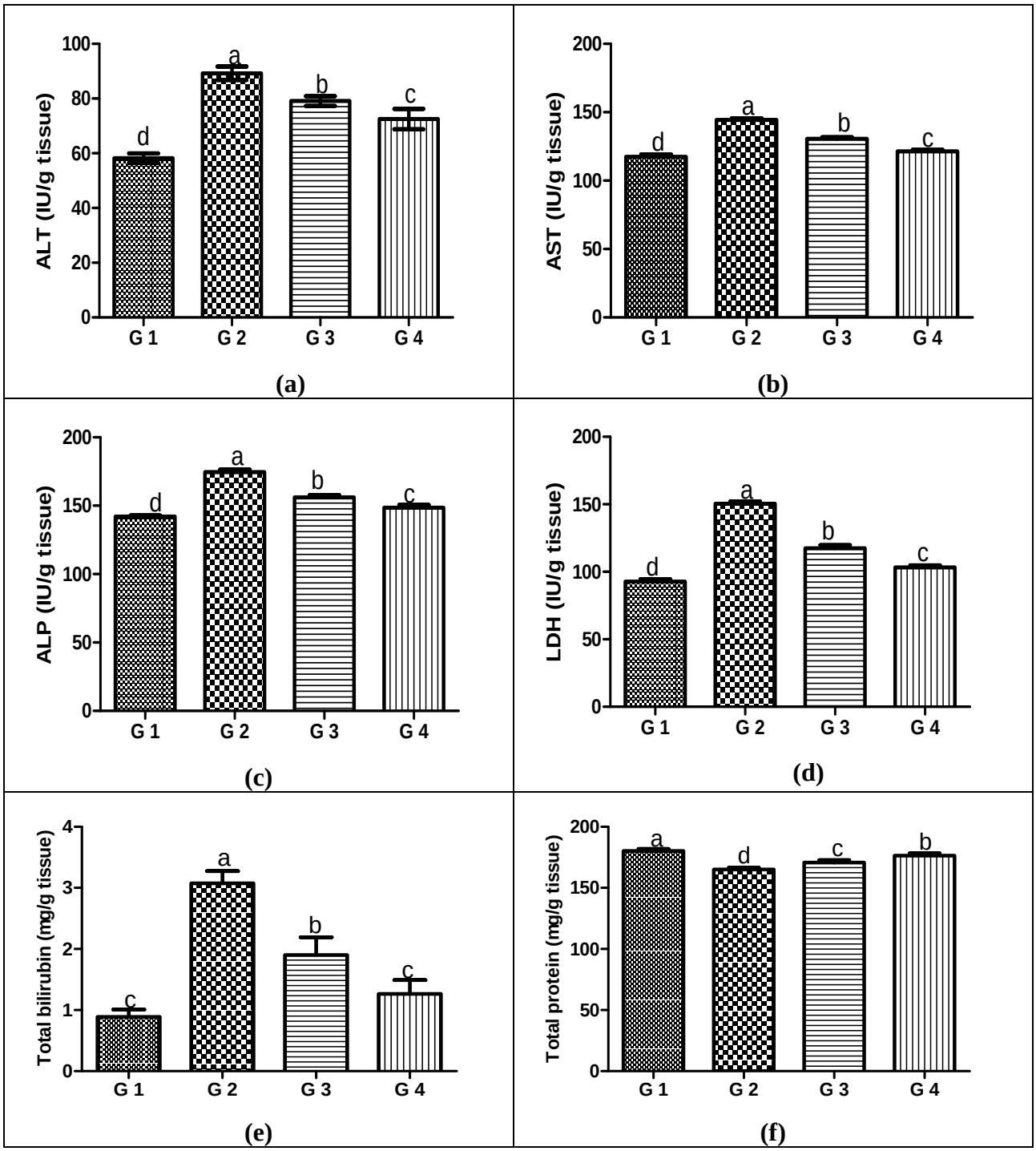


Figure 1: Protective effect of NAC administration against sodium dichromate-induced liver toxicity in rats; a) ALT b) AST c) ALP d) LDH e) Total bilirubin f) Total protein. Columns are Mean ± SD (n=10). Columns with different superscripts are statistically different at P < 0.05. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase.

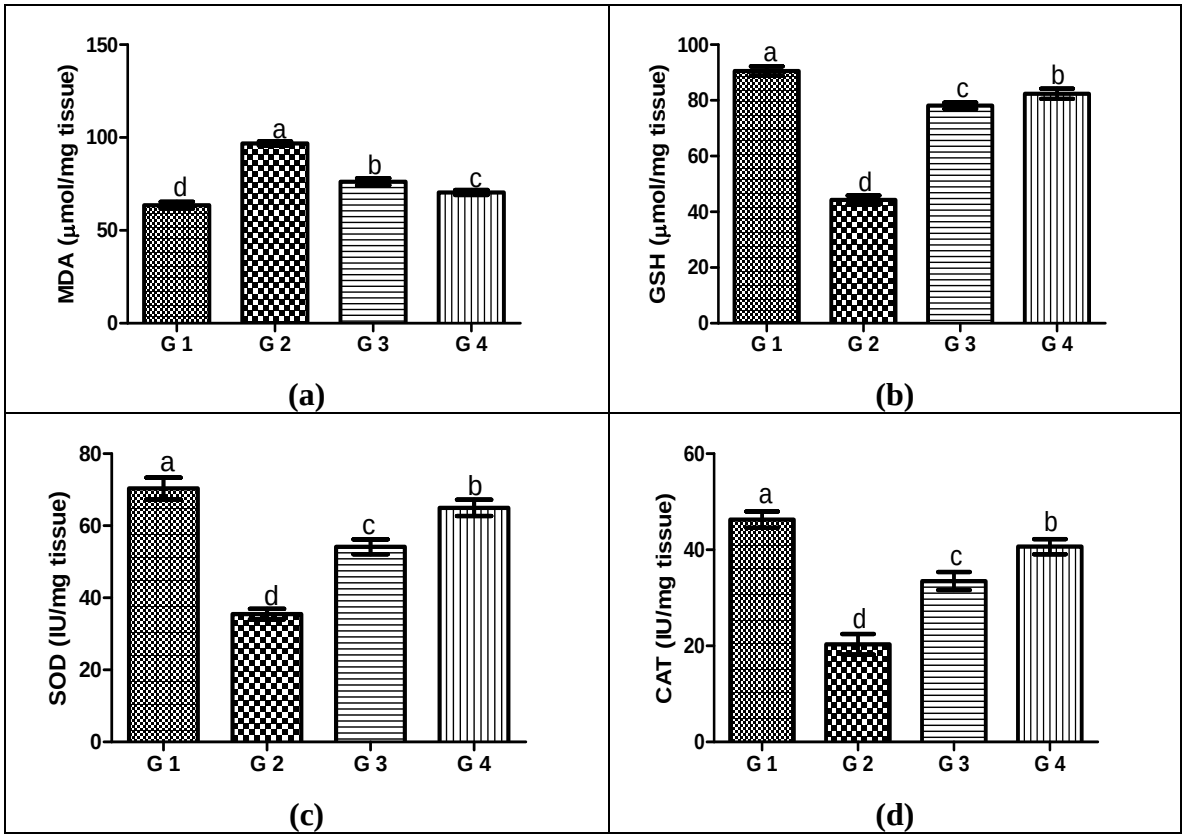


Figure 2: Protective effect of NAC administration against sodium dichromate-induced oxidative damage in rats; a) MDA b) GSH c) SOD d) CAT. Columns are Mean ± SD (n=10). Columns with different superscripts are statistically different at P < 0.05. MDA: Malondialdehyde, GSH: Reduced glutathione, SOD: Superoxide dismutase, CAT: Catalase.

3.3. Effects of NAC administration on the lipid peroxidation and biomarkers of oxidative damage in rat exposed to sodium dichromate

Administration of sodium dichromate (10 mg/Kg) caused alterations in the level of lipid peroxidation and hepatic antioxidant biomarkers; malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT), in the liver of control and experimental rats are shown in Fig. 2. A significant ($P < 0.05$) increase in the level of MDA and significant ($P < 0.05$) decrease in the level of GSH and the activities of superoxide dismutase (SOD) and catalase (CAT) in rats treated with sodium dichromate when compared to normal control rats. However, co-treatments of sodium dichromate along with NAC (25–50 mg/kg) significantly ($P < 0.05$) ameliorates the situation to near normalcy when compared to rats group treated with sodium dichromate alone. The restoration of hepatic antioxidant biomarkers by NAC exhibits dose-dependent relation when compared with sodium dichromate-treated rats.

3.4. Effects of NAC administration on the biomarkers of renal function in rat exposed to sodium dichromate

The results of serum urea and creatinine showed that, administration of sodium dichromate (10 mg/kg) in rats caused significant ($P < 0.05$) increase in serum urea and creatinine levels when compared to normal control group (Fig. 3). But, co-administration of sodium dichromate along with NAC (25–50 mg/kg) significantly ($P < 0.05$) reverses this alteration in a dose-dependent manner when compared to rats group treated with sodium dichromate alone.

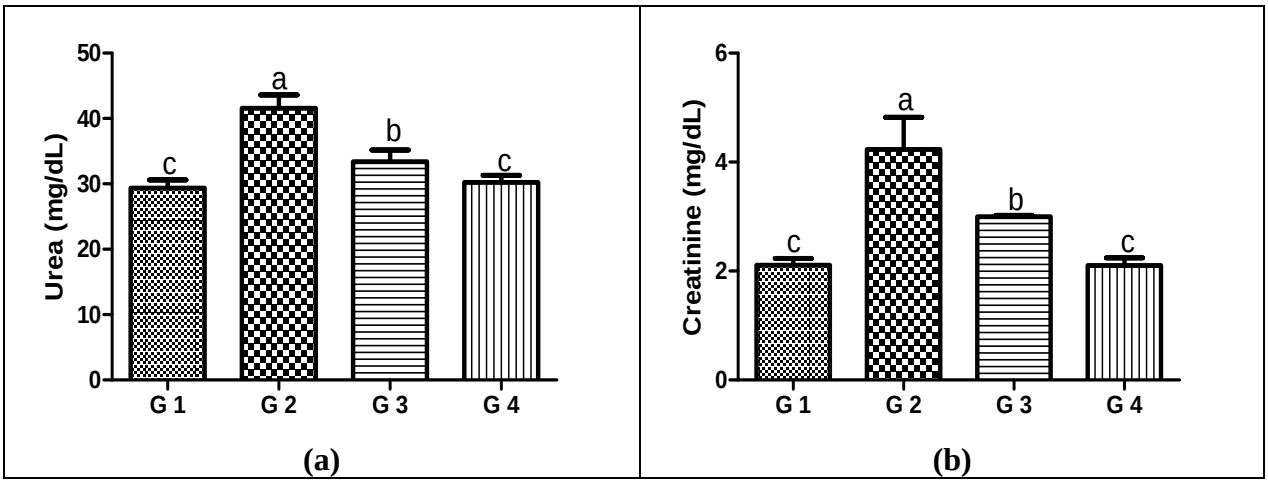
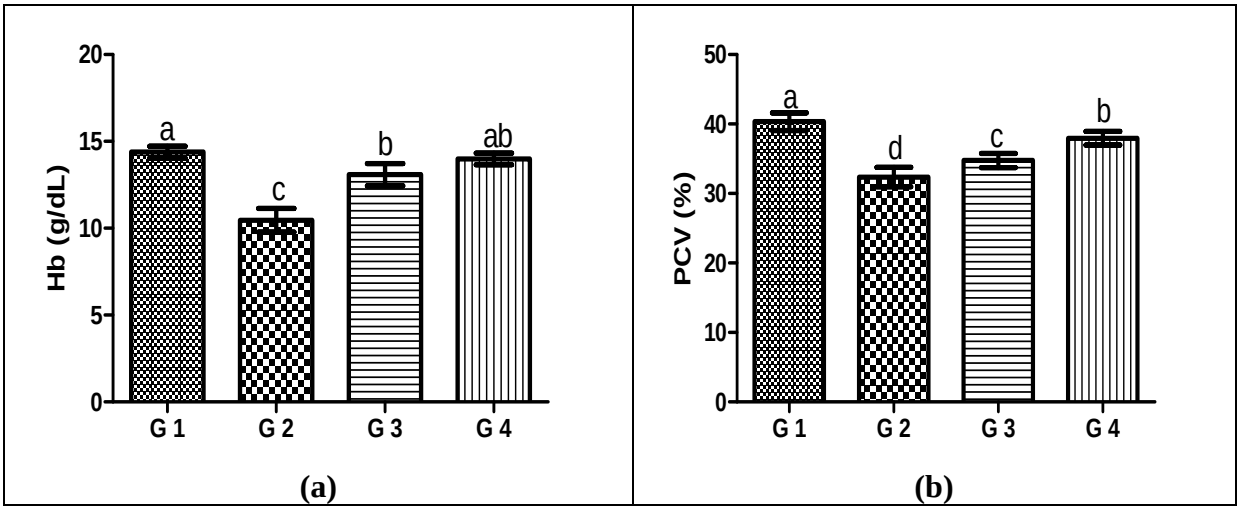


Figure 3: Protective effect of NAC administration against sodium dichromate-induced-renal dysfunction in rats; a) Urea b) Creatinine. Columns are Mean ± SD (n=10). Columns with different superscripts are statistically different at $P < 0.05$.



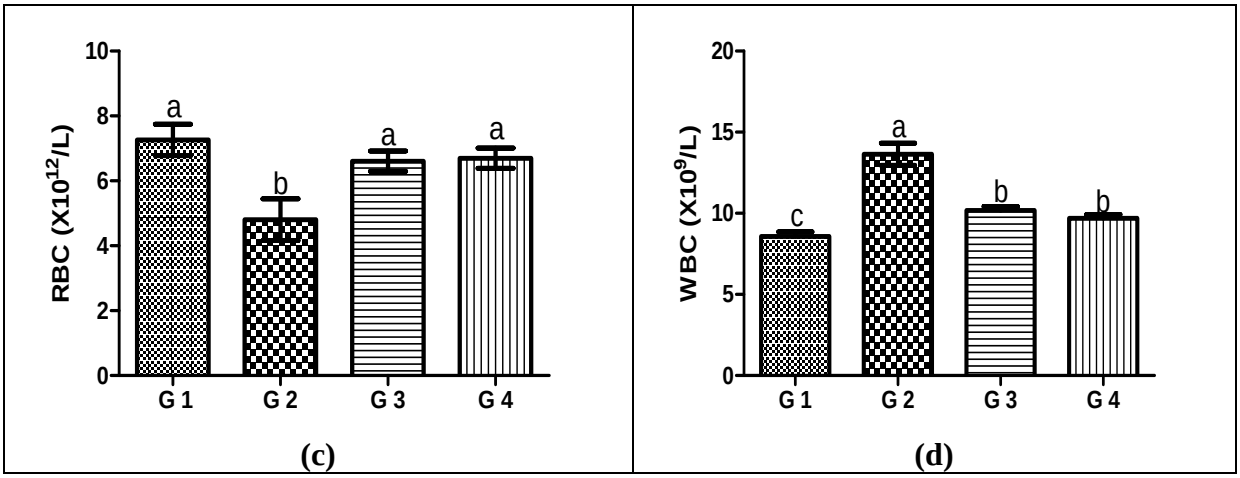


Figure 4: Protective effect of NAC administration against sodium dichromate-induced haematological alterations in rats; a) Hb b) PCV c) RBC d) WBC. Columns are Mean ± SD (n=10). Columns with different superscripts are statistically different at P < 0.05. Hb: Haemoglobin, PCV: Packed cell volume, RBC: Red blood cells, WBC: White blood cells.

3.5. Effects of NAC administration on the haematological parameters in rat exposed to sodium dichromate

Oral administration of sodium dichromate (10 mg/kg)in rats, resulted in significant ($P < 0.05$) decline in the level of plasma hemoglobin (Hb), packed cell volume (PCV), red blood cells (RBC) and a significant increase in white blood cells (WBC) as shown in Fig. 4. Co-administration of sodium dichromate along with NAC (25–50 mg/kg) significantly ($P < 0.05$) rescue the haematological alterations in a dose-dependent relation to near normalcy when compared to rats group treated with sodium dichromate alone.

4. DISCUSSION

Chromium compounds are widely used in industrial and chemical processes such as stainless steel manufacturing, welding, paint and pigment producing, metal finishing, tannery and wood preservation.[23] Occupational exposure to hexavalent chromium compounds such as sodium dichromate, potassium dichromate and ammonium chromate are highly toxic and can induced carcinogenicity, genotoxicity immunotoxicity, neurotoxicity and dermatotoxicity.[24] Also, sodium dichromate generates reactive oxygen species (ROS) during its reduction in successive oxidation states. ROS can cause injury to cellular proteins, lipids, and DNA leading to astute known as oxidative stress.[25, 26] The adverse effects of ROS are balanced by the antioxidant action of enzymatic and non-enzymatic antioxidant system. The role of oxidative stress in injury associated with hexavalent chromium exposure suggests that

antioxidant supplementation may mitigate chromate-induced toxicity.[27] N-Acetyl cysteine (NAC), which is used as a mucolytic agent, is a thiol compound and a membrane-permeable precursor of glutathione, which interacts directly with intracellular oxidants. Also, NAC has the capacity to inhibit several inflammatory elements related to oxidant stress and is involved in the pathophysiology of inflammation.[28, 29] The present study revealed that, administration of sodium dichromate significantly reduced body weight of the rats in a dose-dependent manner indicating its ability to induce oxidative stress. Similar observation was reported by Priti *et al.*,[30] Also, Kumar and Roy.[31] reported that, chromium induced reduction in body weight of rats. Interestingly administration of NAC at 25mg/kg (low dose) and 50 mg/kg (high dose) alleviates the reduction in body weight of rats when compared to non-treated group. Although, restoration of rats body weight was more at higher dose of NAC than the lower dose. Similarly, sodium dichromate administration in rats induced significant alterations in liver and kidney functions as evident by significant increase in the activities of ALT, AST, ALP, LDH and elevation of total bilirubin level along with reduction of total protein in liver tissue. Similarly, increased in serum urea and creatinine is an indicator of kidney damage. Our findings showed sodium dichromate induced significant increase in urea and creatinine levels. Increased liver tissue activity of ALT, AST, ALP and LDH is an indicative of hepatocellular damage since the disruption of the plasma membrane leak intracellular enzymes into the blood stream.[32] LDH is a presumptive marker of necrotic lesions in the hepatocytes whereas bilirubin accumulation is attributed liver dysfunction.[33] Administration of NAC prevented the increase in the above-mention biomarkers of liver damage, demonstrating the hepatoprotective effect of NAC against the sodium dichromate-induced damage. The mechanism through which NAC to prevent hepatotoxicity could be associated with its antioxidant property by enhancement of thiol antioxidant capacity which has been reported to be more effective than calcium EDTA or dimercaptosuccinic acid for clearance and/or excretion of chromium in rats.[34] Sodium dichromate induces oxidative stress through enhanced ROS production leading to genomic DNA damage and oxidative deterioration of lipids and proteins. Our results showed a significant increase in peroxidation marker such as MDA level and significant decrease in GSH level as well as decrease in the antioxidant activity of SOD and CAT in liver of sodium dichromate-treated rats. These findings are in agreement with other studies, which reported that mice treated with cadmium, mercury, showed significant decreases in liver GSH levels due to decreased antioxidant enzymes, where oxidative stress in animal tissues may cause oxidative catabolic effects leading to elevated lipid peroxidation in tissues accompanied with depletion tissue GSH[35,36]

Ercal *et al.*,[37] reported enhancement of lipid peroxidation in rat livers after heavy metal poisoning with mercury, molybdenum, copper, Cr, and manganese. Moreover,[38] Bagchi *et al.*, showed that chromium (VI) induces increase in hepatic mitochondrial and microsomal lipid peroxidation. NAC exhibits direct and indirect antioxidant properties. Its free thiol group is capable of interacting with the electrophilic groups of ROS.[39, 40] This interaction with ROS leads to intermediate formation of NAC thiol, with NAC disulphide as a major end product.[41] In addition, NAC exerts an indirect antioxidant effect related to its role as a GSH precursor. Our results showed oral administration of sodium dichromate caused decrease in haemtological parameters such as Hb, PCV and RBC and alters WBC count. The present finding was in agreement with the study of Kim et al.,[42] Red blood cell chromium is presently, considered the best marker and indicator of hexavalent chromium exposure.[43] Administration of hexavalent chromium leads to a dose-dependent decrease in erythropoietic indices in fishes[44] and in mice.[45] It was reported earlier that Cr (VI) can penetrate membrane of erythrocyte rapidly and enter the cell and accumulates in erythrocytes of exposed workers.[46, 47] Karmakar *et al.*,[48] reported significant decrease in hematological parameters in rats exposed to CdCl2. The reduction in Hb content may be due to increased rate of destruction or reduction in the rate of formation of erythrocytes. In addition, the reduction in PCV and RBC may be attributed to hyperactivity of bone marrow leading to production of red blood cells with impaired integrity that gets easily destroyed in the circulation.[49]

CONCLUSION

Sodium dichromate induced the formation of free radicals and caused oxidative damage in rats by reducing enzymatic and non-enzymatic antioxidant capacity. However, supplementation of rats with NAC ameliorates the situation. This study suggests that oral NAC administration has mitigation effect against sodium dichromate induced-haemato-biochemical alterations in rats.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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