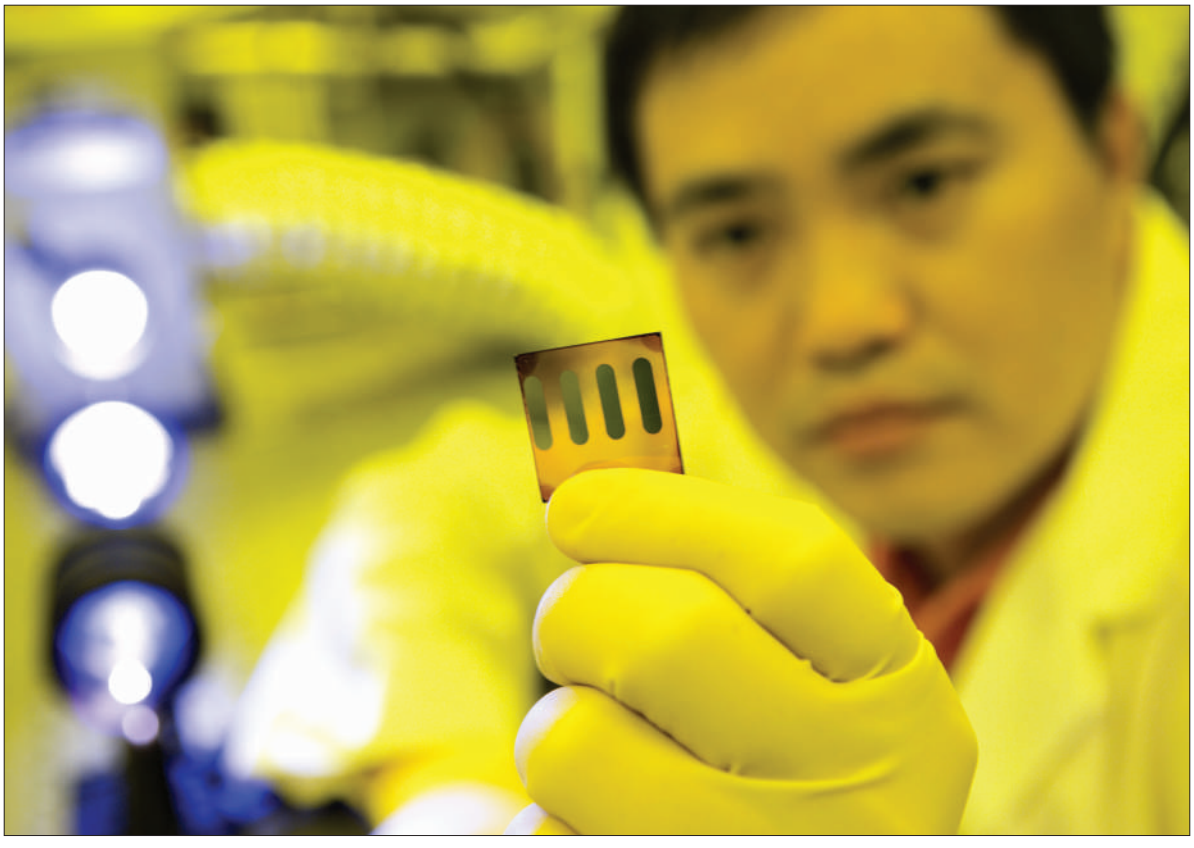

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Research Article
Effect of *Curcuma longa* (Turmeric) Against Potassium Bromate-induced Cardiac Oxidative Damage, Hematological and Lipid Profile Alterations in Rats

Johnson Olaleye Oladele, Oyedotun Moses Oyeleke, Olaide Oladimeji Awosanya and Oluwaseun Titilope Oladele

Biochemistry Unit, Department of Chemical Sciences, Faculty of Sciences, Kings University, Ode-Omu, Nigeria

Abstract

Background and Objective: Food additives have been implicated in the pathogenesis of many human diseases. Such of these food additives is potassium bromate which is used in bakery processings. This study aimed at investigating the effects of ethanolic extract of *Curcuma longa* (CL) against potassium bromate ($KBrO_3$)-induced cardiac oxidative damage, hematological and lipid profile alterations in animal study. **Materials and Methods:** Twenty-four Wistar albino rats were randomized into four groups of 6 animals each. Group 1 (control) received distilled water orally while group 2, 3 and 4 were exposed to 100 mg kg^{-1} b.wt. of $KBrO_3$ orally for 14 days to induce tissue damage. However, group 3 and 4 were administered 100 and 200 mg kg^{-1} b.wt. of CL, respectively for 2 weeks. **Results:** Results showed that $KBrO_3$ significantly reduced the heart weight, body weight gained. Also, $KBrO_3$ significantly ($p = 0.05$) induced oxidative damage in heart with decrease in cardiac reduced GSH, ascorbic acid, catalase, but increase in malondialdehyde (MDA) level. Pancytopenia was also induced by $KBrO_3$ with concomitant marked decrease in levels of HCT, HB, WBC, RBC counts, MCH, monocyte, eosinophils, leukocyte and other platelets. $KBrO_3$ also alter lipid profile with a marked decrease in HDL-Cholesterol and increase in LDL-Cholesterol, CHD risk ratio and total cholesterol compared to the control group. However, Treatment with 100 and 200 mg kg^{-1} b.wt., of CL significantly mitigated against all the deleterious effects caused by $KBrO_3$ by restoring the antioxidant status, maintaining the lipid profile via elevation of the good cholesterol (HDL) and enhance hematological homeostasis. **Conclusion:** These activities exhibited by CL in this study justify its folkloric usage in treatment/management of patients suffering from cardiovascular-related disorders.

Key words: Cardiac oxidative damage, hematological alterations, dyslipidemia, potassium bromate, *Curcuma longa*

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Corresponding Author: Johnson Olaleye Oladele, Biochemistry Unit, Department of Chemical Sciences, Faculty of Sciences, Kings University, Ode-Omu, Nigeria

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Potassium bromate ($KBrO_3$) is known to for its usage in improving bread dough and as food additives for many decades, especially in the later stage of the baking process[1,2]. It is also formed as a byproduct in water ozonized using bromide. Biotransformation of $KBrO_3$ releases free radicals causing oxidative damage to vital biomolecules promoting carcinogenesis and nephrotoxicity in animal studies[3]. Industrial usage of $KBrO_3$ in manufacturing and food processing companies has been banned in some nations such as United Kingdom, Canada including Nigeria in 1990, 1994 and 1993, respectively[2]. However, compliance has not been effectively and fully monitored in some countries leading to detrimental effects on consumers.

Scientific reports have documented that exposure of experimental animals to $KBrO_3$ significantly reduced total reticulocyte, leukocyte and platelet counts in the plasma samples[4,5]. Marked reduction in RBCs, WBCs and platelets could mean selective systemic toxicity caused by $KBrO_3$. Mohamed and Saddek[6] observed that reduced RBC count in their study was possibly due to damaging effects of $KBrO_3$ on bone marrow and hematopoietic organs. Damage to RBC membrane and subsequent impairment is linked to oxidative stress. It also contributes to deformed RBCs removal from circulation by macrophages[7]. Dhembare and Dale[8] reported that $KBrO_3$ induced a significant reduction in WBCs and RBCs count as well as other hematological parameters (e.g., Hb, HCT and MCV). $KBrO_3$ had been shown in various toxicological studies to affect nutritional valve of bread as some key bread vitamins are degraded[9,10].

Lipid profile is a crucial clinical diagnostic tool for many disease cases. Peculiar to the coronary artery disease is reflective of an increased level of LDL and deficiency of HDL[11]. Several studies have linked high level of LDL and high level of HDL, with higher risk of atherosclerosis and reduced incidence of cardiovascular disorders respectively[12,13]. The raised ratio of LDL to HDL caused by $KBrO_3$ may implicate increased tendency for atherosclerosis development.

Curcumin (sourced from *Curcuma longa)* is brightly yellowish in colour, a family of Zingerberaceae[14]. It is a non-polar polyphenolic compound which covers much protection on cells possibly due to antioxidant activities[15,16]. At low doses (about 5 μg mL^{-1}) it possesses anti-genotoxic properties and at higher doses (higher than 8 μg mL^{-1}) it induces genotoxicity. It has chemopreventive roles due to its anti-oxidative, anti-inflammatory, immunomodulatory and pro-apoptotic potential[17]. It is reported to possess anti-tumor potential via modulating critical genes[18,19]. Thus, this present study focused on investigating the ameliorating effects of ethanolic extract of *Curcuma longa* against $KBrO_3$-induced alterations on the lipid profile in plasma, oxidative stress and various hematological parameters in experimental study.

MATERIALS AND METHODS

Chemicals and reagents: Lipid profile kits used (total cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol) are products of Randox Laboratories Limited, United Kingdom. All other chemicals are of analytical grade and were obtained from Analar BDH Limited, Poole, England.

Plant materials and extract preparation: Freshly harvested *Curcuma longa* L. rhizomes were sourced in a farm at Gbongan, Osun State, Nigeria. The authentication of the samples was done in the Biology Department of Federal University of Technology, Akure, Nigeria where a voucher specimen was deposited. This study is carried out between January and June 2019. These rhizomes were oven dried at 45°C to constant weight and subsequently pulverized. Thereafter, the sample was defatted in petroleum ether using soxhlet apparatus. The extract subsequently used for the study was produced by extracting the defatted *Curcuma longa* sample for 72 h in 90% ethanol. The mixture obtained was filtered and the filtrate concentrated at 80°C using rotary evaporator. The paste obtained was weighed and reconstituted in water for subsequent studies.

Animals: Twenty-four Wistar strain albino rats weighing 150-160 g were used for this study. They were sourced and raised at the Biochemistry breeding colony of the Biochemistry unit, Department of Chemical Sciences, Kings University, Ode-Omu, Osun State, Nigeria. Animals were kept under ambient standard conditions (25±2°C and relative humidity of 50±15%) in stainless steel cages and metabolic wastes were cleaned twice daily. The rats were allowed to acclimatize to these conditions for 14 days and were exposed to 12 h daylight and darkness cycle, fed with commercially available rat pellet and water *ad libitum.* This study confirms to the NIH guide for the use and care of laboratory animals and the study was approved by the Institution's Ethical Committee.

Experimental design: The animals were randomized into 4 groups containing 6 rats each. Group 1 (control) received distilled water orally while groups 2, 3 and 4 were administered 100 mg kg^{-1} b.wt. of Potassium Bromate ($KBrO_3$) orally for 14 days to induce oxidative damage. In addition, groups 3 and 4 were exposure to 100 and 200 mg kg^{-1} b.wt. of the ethanolic extract of *Curcuma longa* (CL) via oral administration, respectively for 2 weeks.

Blood collection and preparation of serum: The rats were sacrificed 24 h after the last dose has been administered by cervical dislocation. The blood samples were collected via direct heart puncture into sterile dry centrifuge tube. These blood samples were allowed to cloth at room temperature for 10 min and then spinned at 4,000 rpm in an MSC (Essex, UK) bench centrifuge. The clear supernatant (serum) was transferred into clean dry sample bottles aspirated Pasteur pipette and then stored at -4°C for further analyses.

Tissues homogenates preparation: The hearts were immediately removed from the rats, blotted to remove blood stains. These tissues were then cleansed in 1.15% KCl to remove haemoglobin, weighed and homogenized in ice-cold 10 mM potassium phosphate buffer, (pH 7.4) using the Teflon homogenizer. The homogenates were centrifuged at 12,500 g for 20 min at 4°C to obtain clear post-mitochondrial fractions which were stored until required for analysis.

Measurement of biochemical parameters: Protein content was determined using method reported by Lowry *et al.*[20]. The Ellman's reagent-dependent method of Jollow *et al.*[21] was used to evaluate the reduced glutathione concentration. Oxidative damage was assessed following the protocol reported by Vashney and Kale[22], by measuring the level of malondialdehyde which is a lipid peroxidative product, after forming a pink coloured chromogen upon reacting with 2-thiobarbituric acid. Catalase (CAT) activity was determined based on the method of Sinha[23] which measure the reduction of dichromate in acetic acid to chromic acetate at 570 nm. Ascorbic acid concentration was determined according to the method of Jagota and Dani[24]. The level of superoxide dismutase (SOD) activity was determined by the method of Misra and Fridovich[25] based on the ability of the enzyme to inhibit auto-oxidation of epinephrine at pH 10.2 and 30°C.

Measurement of serum lipid profile: Total cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol were measured in the serum of individual rats using the appropriate methods. Total cholesterol was determined by the enzymatic endpoint method[26]. Triglyceride was assayed using the GPO-PAP method[27] while precipitant method[28] was used in the measurement of HDL cholesterol. The LDL cholesterol was estimated using the procedure earlier described[29]. Coronary heart disease risk ratio (CHD risk ratio) was obtained by calculating the ratio of concentrations of total cholesterol to HDL-cholesterol[30]. Measurement of concentrations was done by the use of Camspec M106 UV spectrophotometer (Ohaus Corporation Pine Brook USA).

Statistical analysis: Data of results were expressed as Mean±SD. Comparison was done using one-way analysis of variance (ANOVA) between the control and treatment groups. The $p<0.05$ were considered statistically significant.

RESULTS

Effect of *Curcuma longa* and $KBrO_3$ on heart and body weight of rats: In Table 1, administration of $KBrO_3$ induced decrease in the heart and total body weight, ethanolic extracts of *Curcuma longa* caused a dose-dependent increase in the heart and total body weight when compare to the bromate treated group.

Influence of *Curcuma longa* on hematological parameters of $KBrO_3$ treated rats: The various hematological parameters investigated were reported in Table 2. Levels of HCT, Hb concentration, RBC, lymphocyte, monocyte significantly decrease ($p = 0.05$) in $KBrO_3$ treated group when compared to the control. However, in the *Curcuma longa* extract groups, these hematological indices increased significantly ($p = 0.05$) in dose dependent manner when compared to the toxicant ($KBrO_3$) group. Others like WBC and MCHC maintained same pattern as compared to the control, they were significantly decreased in $KBrO_3$ groups.

Influence of *Curcuma longa* on $KBrO_3$-induced serum lipid profile alteration: Physiological disorders are fallout of many alterations in lipid profile due to exposure to $KBrO_3$. In this study, Fig. 1-3 showed the results total cholesterol (TC), triacylglycerol (TAG), HDL-cholesterol, LDL-cholesterol and coronary heart disease risk (CHD) ratio. There was marked increase ($p = 0.05$) in total cholesterol, TAG, LDL-cholesterol, CHD risk ratio and concomitant decrease in level of HDL-cholesterol in group administered $KBrO_3$ only. Following treatment with 100 and 200 mg kg^{-1} b.wt. *Curcuma longa* extracts, the level of total cholesterol, TAG, LDL-Cholesterol, CHD Risk ratio and HDL-Cholesterol were all restored significantly in a dose dependent pattern when compared to control group.

Table 1: Body weight gain and brain weight of rats

Experimental groups	Initial body weight (g)	Body weight gain (g)	Heart weight (g)
Control	153.50±4.10	164.00±3.12	0.63±0.10
$KBrO_3$ group	150.02±3.75	160.07±2.33	0.52±0.12
$KBrO_3$+100 mg kg^{-1} b.wt. of CL	155.95±2.84	167.82±2.86	0.56±0.09
$KBrO_3$+200 mg kg^{-1} b.wt. of CL	158.23±5.31	171.25±3.05	0.59±0.06

Values are Means±SD of 6 rats

Table 2: Hematological parameters in rats administered potassium bromate and *Curcuma longa*

Parameters	Group I	Group 2	Group 3	Group 4
HCT (%)	35.01±3.64	20.92±3.78*	25.84±5.13*#	31.61±4.06#
Hb concentration (g dL^{-1})	20.29±3.12	13.04±2.90*	16.09±3.05*#	18.02±3.05#
RBC ($\times 10^6$ µL)	7.84±0.38	2.99±0.72*	4.44±0.35*#	6.16±0.82#
WBC ($\times 10^3$ µL)	14.24±2.17	8.92±2.01*	12.80±1.91*#	13.60±2.02*#
MCV (fL)	70.95±5.87	46.93±5.77*	54.09±6.01*#	62.02±6.13*#
MCHC (g dL^{-1})	45.05±5.07	32.06±4.03*	38.51±4.12*	41.36±4.97*#
Lymphocyte (%)	20.08±4.15	13.81±2.73*	16.14±2.72*#	18.05±2.51#
Reticulocytes (%)	13.99±2.38	9.78±3.29	10.89±2.33*	13.07±2.61#
Monocyte (%)	55.47±5.05	41.27±4.57*	48.14±4.96*#	52.40±5.01#
Eosinophil (%)	13.04±2.67	9.06±1.26*	10.20±1.04	10.52±1.42*
Neutrophil (%)	29.93±4.07	20.01±4.18*	25.79±4.50*#	27.40±4.66*#
Basophil (%)	9.32±1.09	4.51±0.92*	7.76±0.53*#	8.19±1.03

Data presented as Mean±SD of 5 animals each per group, RBC: Red blood cell count, WBC: White blood cell count, MCHC: Mean cell haemoglobin concentration, MCV: Mean cell volume, *Significantly different from normal control group at p<0.05, #Significantly different from group 2 at p<0.05

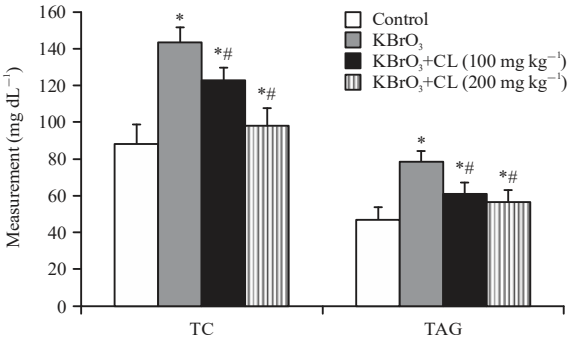

Fig. 1: Ethanolic extract of *Curcuma longa* reduced $KBrO_3$-induced raise in TC and TAG

*Significantly different from normal control group at p<0.05, #Significantly different from $KBrO_3$-treated group at p<0.05

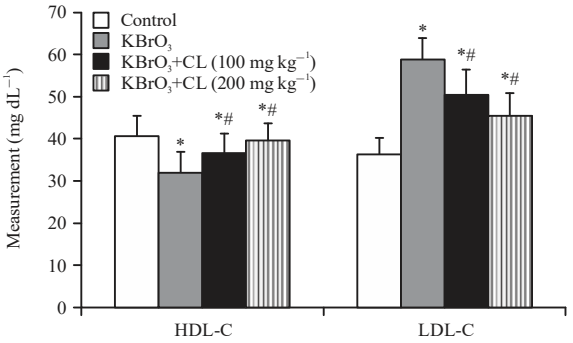

Fig. 2: Ethanolic extract of *Curcuma longa* promoted the good cholesterol (HDL-C) and reduced the bad cholesterol (LDL-C)

*Significantly different from normal control group at p<0.05, #Significantly different from $KBrO_3$-treated group at p<0.05

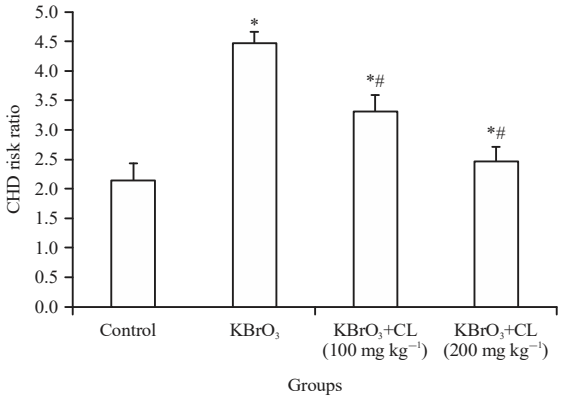

Fig. 3: Ethanolic extract of *Curcuma longa* suppressed $KBrO_3$-induced risk of coronary heart risk

*Significantly different from normal control group at p<0.05, #Significantly different from $KBrO_3$-treated group at p<0.05

Influence of *Curcuma longa* on cardiac oxidative damage mediated by $KBrO_3$ in rats: Malondialdehyde (MDA), an indication of lipid peroxidation was significantly (p = 0.05) increased in $KBrO_3$ treated group compared to the control (Fig. 4). Treatment with 100 and 200 mg kg^{-1} b.wt., *Curcuma longa* extracts caused a significant (p = 0.05) decrease in the MDA level. Similarly, $KBrO_3$ affected both enzymatic and on-enzymatic antioxidants (Fig. 5, 6). Levels of reduced glutathione (GSH), ascorbic acid, catalase and superoxide dismutase (SOD) were decreased significantly in $KBrO_3$ treated group compared to the control. Treatment with 100 and 200 mg kg^{-1} b.wt., *Curcuma longa* extracts caused significant increase in all the antioxidant markers in a dose

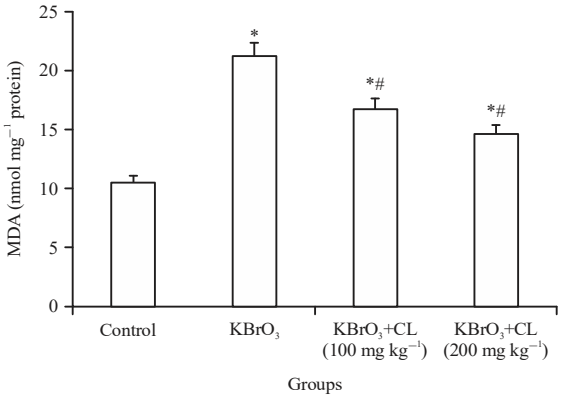

Fig. 4: Ethanolic extract of *Curcuma longa* prevented $KBrO_3$-induced oxidative damage

*Significantly different from normal control group at p<0.05, #Significantly different from $KBrO_3$-treated group at p<0.05

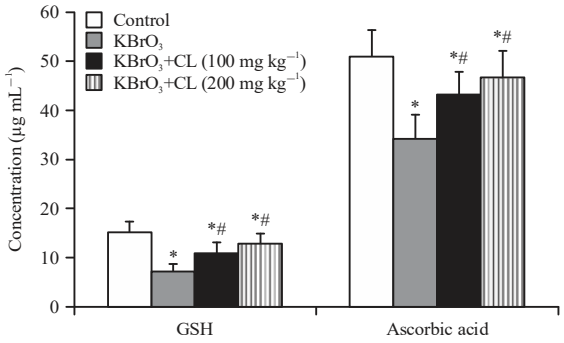

Fig. 5: Ethanolic extract of *Curcuma longa* prevented $KBrO_3$-induced inhibition of reduced glutathione and ascorbic acid

*Significantly different from normal control group at p<0.05, #Significantly different from $KBrO_3$-treated group at p<0.05

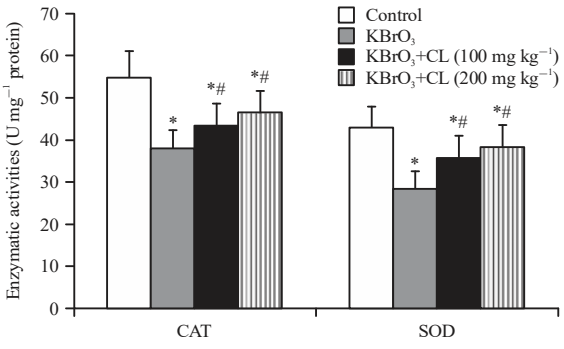

Fig. 6: Ethanolic extract of *Curcuma longa* improved $KBrO_3$-induced inhibition of antioxidant enzymes activities

*Significantly different from normal control group at p<0.05, #Significantly different from $KBrO_3$-treated group at p<0.05

dependent pattern. Enzymatic antioxidants were significantly reduced in all groups when compared to the control. Dose dependently, they increased significantly in the treatment groups compared to $KBrO_3$ group, Similarly.

DISCUSSION

Potassium bromated ($KBrO_3$) undergoes reduction in its role in improving bread dough and in cosmetic products (like dyeing of textiles and stable hair weaver) and also cause pollution in water. In relation to its damaging role in some vital organs, United States among other has banned its usage[31,32]. This study focused on investigating the ameliorating effects of ethanolic extract of *Curcuma longa* against $KBrO_3$-induced alterations in the lipid profile, oxidative stress and hematological distortions in animal model. We observed marked decrease in heart weight and total body weight gained in $KBrO_3$ treated group compared to the control. The weights were restored in the treatment groups in a dose dependent manner. This could be as a result on the potential of *Curcuma longa* to cause a rebound in the weight of certain key organs. This tandem with previous results reported by Oyewole and Oladele[33] that plant extract can enhance organ and rat growth by increasing feeding efficiency and appetite, enhancing nutrient biotransformation and utilization.

The results of this study showed that Hb concentration, Red blood cell count, monocyte and HCT counts of the $KBrO_3$ treated group decreased significantly (p = 0.05) when compared to the control. However, treatment with chosen doses of ethanolic extract of *Curcuma longa* increased significantly the parameters in a dose dependent manner. The observed decrease in the platelet counts, RBC, lymphocyte count could be due to oxidative damage in the DNA strands mediated by oxidative stress[4,5,34] from $KBrO_3$, therefore, the reductions reported could imply selective systemic toxicity caused by $KBrO_3$. This agrees with the previous findings that some xenobiotics are capable of causing general reduction in the blood cellular contents[30,35]. *Curcuma longa* protective effects suggest its influence on hematopoietic and immunomodulatory activities.

In clinical practices, alteration in lipid profile is an indication of pathological conditions relative to the cardiac disorder. Sedimentation of plaques in the arterial walls caused atherosclerosis which featured as increase level of low density lipoprotein (LDL) and decrease level of high density lipoprotein (HDL)[11]. Exposure of rats to $KBrO_3$ in this present study caused marked decrease in HDL and increase in LDL levels. Levels of HDL and LDL determine chances of

developing diseases[36]. The significant increase in serum LDL levels may result from the activity of its receptor being suppressed[37], accounting for increased VLDL conversion to LDL, causing eventual overproduction and accumulation of LDL[37].

Similarly, the levels of triacylglycerol (TAG) and total cholesterol were increased significantly in the $KBrO_3$ group causing elevation in atherogenic index, a good prediction for developing atherosclerotic disorders. Increased CHD risk ratio caused by $KBrO_3$, may imply increase tendency for the development of atherosclerosis. Treatment with chosen doses of ethanolic extract of *Curcuma longa* significantly attenuates all the alterations in the lipid profile. This result agrees with previous report of Bello *et al*.[38], who documented protective effects of plant extracts against atherosclerosis. *Curcuma longa* interferes with cholesterol uptake in intestine via its elevated diversion to bile acid metabolism and its excretion or by interfering with cholesterol absorption exogenously[39]. Good cholesterol, HDL also mop up the LDL, thereby cleaning arterial walls of plaques.

Reduced glutathione (GSH) and ascorbic acid are non-enzymatic antioxidants used to withstand/inhibit oxidative stress and cellular insults from foreign toxic chemicals. Exposure of rats to $KBrO_3$ caused marked decrease in cardiac level of reduced glutathione (GSH) and ascorbic acid. However, treatment with ethanolic extract of *Curcuma longa* significantly ameliorate the anomalies. Also, catalase and superoxide dismutase which are enzymatic antioxidants were significantly reduced upon treatment with $KBrO_3$ and later restored in the *Curcuma longa* treatment groups in a dose dependent manner, due to its ability to significantly increase activity of acyl-CoA oxidase of treated hypercholesterolemic rats[40]. Central to cholesterol metabolism is the role played by cholesterol-7a-hydroxylase, *Curcuma longa* is shown to be hypocholesterolemic in activity by increasing this core enzyme's activity, eventually rate of cholesterol metabolism is elevated[41]. *Curcuma longa* acts as inhibitors of lipid peroxidation as evident in decreased MDA values for both treatment groups, leading to decrease in cholesterol[42,43]. *Curcuma longa's* ability to significantly lower cholesterol and TAG concentrations may be as a result of dietary turmeric potentials to lower lipid peroxidation by enhancing the activities of antioxidant enzymes[44].

CONCLUSION

Taken together, our data revealed that $KBrO_3$ possesses numerous deleterious effects on the cardiac redox status, disruption lipid profile and hematological parameters and reduction in organ and body weight. However, administration of ethanolic extract of *Curcuma longa* has capacity to savage the deleterious effects created by $KBrO_3$ by restoring the antioxidant status, maintaining the lipid profile via elevation the good cholesterol (HDL) and enhance hematological homeostasis. These properties of *Curcuma longa* make it a potential material in reducing deleterious effects of $KBrO_3$.

SIGNIFICANT STATEMENT

This study reveals the beneficial effects of *Curcuma longa* in the management/treatment of cardiovascular related diseases. These results show the deleterious effects of $KBrO_3$ on cardiac redox status, disruption lipid profile and hematological parameters and reduction in organ and body weight. However, treatment with ethanolic extract of *Curcuma longa* mitigated against harmful effects induced by $KBrO_3$ by restoring the antioxidant status, maintaining the lipid profile via elevation the good cholesterol (HDL) and enhance hematological homeostasis.

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