IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB)
ISSN: 2455-264X, Volume 10, Issue 3 Series 1 (May. – June. 2024), PP 42-53
www.iosrjournals.org

Abatement Of Potassium Bromate Induced Hepatorenal Toxicity And Altered Biochemical Indices In Male Wistar Rats Using Ethanol Leaf Extract Of Irvingia Gabonensis

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Abstract
The renal toxicity associated with potassium bromate ($KBrO_3$) treatment in both animals and humans have been reported. Irvingia gabonensis a perennial plant belonging to the family Irvingiaceae is known to elicit beneficial health effects. However, the influence of Irvingia gabonensis on the renal and hepatotoxicity associated with $KBrO_3$ induced nephrone toxicity is unavailable in the literature. The current study evaluated the effects of Irvingia gabonensis on the dysfunctional renal and liver status triggered by KBrO3 exposure in rats. Experimental animals were exposed to $KBrO_3$ (50mg/kg), co-treated with Irvingia gabonensis (500 mg/kg) and (1000 mg /kg) for 14 days. Results revealed that Irvingia gabonensis treatment significantly assuaged $KBrO_3$-mediated oxidative-inflammatory response. Additionally, Irvingia gabonensis attenuated $KBrO_3$ - induced reduction in antioxidant enzyme activities and enhanced hepatic-renal function markers, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and levels of urea and creatinine. Irvingia gabonensis efficiently mitigated $KBrO_3$-mediated increase in myeloperoxidase (MPO) activity, levels of interleukin-b (IL-6), Tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) in kidney of rats. In conclusion, Irvingia gabonensis ameliorated deficits in the renal function in KBrO3-exposed rats by lowering the levels kidney function markers via diminution of oxidative-inflammatory stress.

Keywords: *Potassium Bromate, Irvingia gabonensis, Kidney, Histopathology, Oxidative stress, inflammatory stress.*

Date of Submission: 27-05-2024 Date of Acceptance: 07-06-2024

I. Introduction

Irvingia gabonensis is an african plant commonly called 'African mango' or "Wild mango" and is an indigenous forest tree (Muhammad et al, 2021). It belongs to the *Irvingiaceae* family of plants (Matos *et al.*, 2009). *Irvingia gabonensis*, is known for its potential therapeutic benefits in managing diabetes and obesity, as well as its analgesic, antimicrobial, antioxidant, and gastrointestinal properties (Okereke *et al.,* 2023), Traditionally the leaves of the plant is used for the treatment of diabetes while the seeds are used for 'African soup' and is believed to have antidiabetic effects (Atanu *et al.,* 2022). Studies by Adamson *et al.,* 1990 reported that seeds of *Irvingia gabonensis* were shown to cause a reduction in plasma lipids and an increase in HDL-cholesterol. Based on available experimental evidence, it is proven that the leaves and stem extracts of Irvingia regulate blood glucose and lipid profile (Sulaimon *et al.,* 2015). Studies have also reported the effectiveness of extracts from *Irvingia gabonensis* against toxicity from various chemical agents (Gbadegesin *et al*., 2014; Olorundare *et al.,* 2020). Studies by Atanu *et al.,* 2022 revealed that the aqueous and ethanol extracts had high phenolic content, antioxidant and α-amylase, and α-glucosidase inhibitory activity. It concluded that the inhibitory effects of the plant extracts on enzymes linked to diabetes namely, α-amylase and α-glucosidase could be due to its phenolic content as well as other bioactive compounds identified by GC-MS analysis. The study provided evidence that inhibition of α-amylase and α-glucosidase is a mechanism by which *Irvingia gabonensis* exerts its antidiabetic effect. Muhammad *et al.,* 2021 reported that *Irvengia gabonensis* seed extract poses nephrocurative effects against acetaminophen induced kidney damage which may be mediated through its antioxidant ability.

Potassium bromate is used as an oxidizer to mature flour during milling and to condition dough during baking. It was also found that active oxygen species were generated in a specific interaction of KBrO3 with rat kidney cells in vitro and KBrO3-induced oxidative stress may lead to an enhancement in cellular proliferation in kidney (De Vico *et al.,* 2018). Studies have suggested that the posssible mechanism of KBrO3-induced carcinogenicity in experimental models includes mutation base modification (8-oxodeoxyguanosine), chromosomal aberrations, and alters gene expression, leading to cancer (Manzoor *et al.,* 2021; Jan *et al.,* 2017; Oayyum *et al.,* 2016). KBrO3 increases lipid peroxidation, the creatinine concentration, and enzyme activity in the sera of rats (Naghma *et al.,* 2004).

Irvingia gabonensis has been shown to protect against various disorders involving oxidative stress, it can be hypothesized that pretreatment of animals with *Irvingia gabonensis* may attenuate KBrO3-mediated renal oxidative stress in Wistar rats. The present study was therefore aimed at investigating the effect of *Irvingia gabonensis* on KBrO3-induced nephrotoxcicity in wistar rats by the determination of biochemical parameters and by histological examination.

II. Material And Methods

Plant materials

Fresh leaves of *Irvingia gabonensis* were collected from Aba in Osisioma local Government, Abia State. The plant was identified, as well as authenticated by a taxonomist, Dr Garuba Omosun of the Department of Plant Science and Biotechnology, Michael Okpara University of Agriculture, Umudike (MOUAU), Abia State, Nigeria. A voucher number: MOUAU/VPP/CVM/118/2023 was assigned to the plant.

Preparation and extraction of plant material

Extraction technique described by Orieke *et al.,* (2019) was adopted. The Fresh leaves were neatly plucked out of the stalk and thereafter, they were air dried at room temperature (25-27oC) for 7 days before being pulverised into fine powder. Certain quantity (350 g) of the powdered sample was weighed and dissolved in 1000ml of ethanol, stirred and kept for 48 hr. Thereafter, it was filtered using a muslin cloth. The resulting filtrate was evaporated to dryness in a water bath at 40°C until all the ethanol had been removed. The dry extract was stored in a refrigerator (4°C) until its usage. The yield of the extract (in percentage) was calculated as:

[Weight of the extract/Weight of the powdered sample] x 100.

The weight of the *Irvingia gabonensis* extract was 34.04 g while the percentage yield was 9.72%.

Acute toxicity study

The new Lorke's method used by Orieke *et al.,* (2019) was adopted with little modification. At the highest tested dose of 5000 mg/kg, no mortality or obvious signs of toxicity was observed. The lethal dose of the extract was therefore obtained as >5000 mg/kg. The LD50 value for *Irvingia gabonensis* was obtained as>5000 mg/kg body weight which was considered to be safe and on this basis, the doses of 500 and 1000 mg/kg for *Irvingia gabonensis* were selected. Also LD50 value for was $KBrO_3$ was obtained as 346.41mg/kg body weight, on this basis the dose 50mg/kg was selected.

Experimental design

Twenty-five male rats of the wistar strain, weighing between 80 and 130g were used. Ethical approval was obtained from the Board of the Department of Biochemistry, Rhema University, Nigeria, Abia State, Nigeria. The rats were acclimatized to their food and water for 2 weeks which they had access to *ad libitum*. Following acclimatization, they were distributed randomly into five groups of five rats each. The following experimental groups (n = 05 rats per group) were studied.

Group I: (Control); the animals were untreated.
Group II: Were treated with $KBrO_3$ (50 mg/kg bw) intragastric daily for two weeks.
Group III: Were treated with oral administration of *Irvingia gabonensis* (1000 mg/kg bw) daily for two weeks.
Group IV: Rats were treated with $KBrO_3$ (50 mg/kg bw) intragastric and oral administration of *Irvingia gabonensis* (500 mg/kg bw) daily for two weeks.
Group V: Rats were treated with $KBrO_3$ (50 mg/kg bw) intragastric and oral administration of *Irvingia gabonensis* (1000 mg/kg bw) daily for two weeks

The body weights of the rats were recorded on a daily basis. At the end of 14 days, the rats were fasted overnight and on the 15th day, they were euthanized by cervical dislocation. Blood was collected by cardiac puncture into plain sample tubes and allowed to clot. Sera were harvested from the clotted blood samples by

centrifuging at 3000 x g for 20 min and used for biochemical analyses. The kidneys and liver were excised, washed with cold normal saline, blotted with filter paper, and weighed on an electronic balance.

After measurements of the kidney weights, two kidneys were selected from each group and processed for histology. The remaining three kidneys from each group were homogenized in ice-cold phosphate buffered saline and centrifuged at 10 000 xg for 15 minutes and the supernatants were analyzed for lipid peroxidation, catalase, reduced glutathione (GSH), superoxide disthmutase (SOD) and glutathione peroxidase (GPx) activities.

The percentage change in the body weights of the rats was calculated as:
{Final body weight -Initial body weight}/Final body weight} -100.

Similarly, the relative organ weights of the rats were calculated as follows:
Relative Kidney weight (g/100 g) = {Total Kidney weight/Final body weight} - 100
Relative Liver weight (g/100 g) = {Total liver weight/Final body weight} - 100
Relative Heart weight (g/100 g) = {Total heart weight/Final body weight} -100

Analysis of serum

Determination of Kidney Biomarkers in the sera

Urea, Creatinine, and Electrolytes concentrations were determined using spectrophotometric techniques using RANDOX Kits and following standard procedure outlined by the manufacturer (Randox Laboratories Limited).

Determination of Liver Biomarkers in the sera

AST, ALP,ALT, Bilirubin, Albumin, Globulin, Total Protein concentrations were determined using spectrophotometric techniques using RANDOX Kits and following standard procedure outlined by the manufacturer (Randox Laboratories Limited).

Determination of lipid profile in the sera

Total cholesterol, TAG and HDL concentrations were determined using spectrophotometric techniques using RANDOX Kits and following standard procedure outlined by the manufacturer (Randox Laboratories Limited). LDL and VLDL concentrations were derived from HDL, TAG and Cholesterol.

Assay for inflammatory markers levels

Interleukin 6 (IL-6), interleukin 1 Beta (IL-1b) concentrations of the rats were determined using ELISA Kit (ELabscience, USA) following the instructions of the manufacturer. Data that were obtained are expressed as pg/ml of protein. TNF-α concentrations of the rats were determined using Rat Tumor Necrosis Factor Alpha ELISA Kit (ELabscience, USA) following the instructions of the manufacturer. Data that were obtained are expressed as pg/ml of protein.

Assay of markers of oxidative stress in the Kidney

Catalase activity was determined in the prostates of the rats using the method of Sinha. SOD activity was determined using the method of Misra and Fridovich. Glutathione peroxidase (GPx) was estimated using the method of Paglia and Valentine. GSH was determined using the method of Beutler *et al.* Lipid peroxidation was determined by measuring the formation of thiobarbituric acid reactive substance (TBARS) using the method of Varshney and Kale.

Liver and Kidney histology

Sections of the fixed liver and Kidney tissues were dehydrated with alcohol, cleared with xylene and embedded in molten paraffin wax. On solidifying, the paraffin blocks were subsequently sectioned at 5μm using a microtome. The sections were subsequently stained with infiltrated Ehrlich hematoxylin for 15 minutes for viewing under a microscope (Ajonuma *et al.,* 2005; Nwauche *et al.,* 2014). Photomicrographs of the tissues were taken with a light microscope at x100 magnification.

Statistical analysis

Data were analyzed statistically using the statistical package for social sciences (SPSS) version 26.0. One-way analysis of variance (ANOVA) was used for comparison of means. Differences between means were considered to be significant when $P < 0.05$.

III. Result

The LD_{50} of *Irvingia gabonensis* leaf ethanol extract was 5000 mg/kg. The body weights and percentage changes in the body weights of the rats investigated in this study are shown in Table 1. The body weights of the normal rats administered IG only (41.96% increase) , IG 500mg/kg (40.37%)or IG 1000mg/kg(46.07% increase) were significantly different ($P > 0.05$) from that of the normal control that recorded 27.91% increase in body weight. However, the body weights of the disease control administered $KBrO_3$only (50 mg/kg) (25.45% increase) were significantly reduced ($P < 0.05$) in comparison with the normal control.

Table 1. Body weights (g) and percentage change of weights of rats

Treatment Groups	Control	$KBrO_3$Only (50 mg/kg)	IG(1000 mg/kg)	$KBrO_3$(50 mg/kg)+IG (500 mg/kg)	$KBrO_3$(50 mg/kg)+IG (1000 mg/kg)
Initial animal weight (g)	91.93±11.93[a]	86.44±32.54[a]	87.76±24.10[a]	72.43±7.47[a]	82.80±13.89[a]
Final animal Weight (g)	117.38±13.44[b]	100.45±23.40[c]	123.00±25.26[a]	104.25±13.60[a]	116.12±11.95[a]
Weight gain (g)	25.52±2.03[b]	14.01±35.79[c]	35.24±1.32[a]	29.15±1.68[a]	33.32±5.11[a]
%Weight gain (g)	27.91±2.30[b]	25.45±41.33[c]	41.96±9.89[a]	40.37±1.79[a]	41.32±10.57[a]

.Values are means ± SD. [a–d]Means with different superscripts along the column are significantly different ($P < 0.05$).

The relative kidney, heart and liver weights (wet weight) of the rats investigated in this study are shown in Table 2. The relative kidney, heart and liver weights of the disease control or the normal rats administered IG were not significantly different ($P > 0.05$) from that of the normal control. Furthermore, the relative kidney, heart and liver weights of the rats administered IG (at both doses) were not significantly different ($P > 0.05$) from that of the disease control.

Table 2: Relative Body, liver, heart and kidney weight in $KBrO_3$ treated rats

Treatment Groups	Control	$KBrO_3$only (50 mg/kg)	IGonly (1000 mg/kg)	KBrO3only (50mg/kg)+IG (500 mg/kg)	KBrO3 only (50mg/kg)+ IG(1000mg/kg)
Animal live Body weight (g)	117.38±13.43[a]	100.45±23.40[a]	123.00±25.26[a]	104.25±13.60[a]	116.12±11.95[a]
Weight of liver (g)	4.55±0.80[a]	3.85±0.80[a]	4.85±0.90[a]	4.20±0.83[a]	4.93±0.22[a]
Weight of Right kidney (g)	0.46±0.05[a,b]	0.41±0.08[a]	0.56±0.08[b]	0.43±0.07[a,b]	0.51±0.08[a,b]
Weight of Left kidney (g)	0.44±0.03[a]	0.46±0.07[a]	0.53±0.09[a]	0.42±0.03[a]	0.49±0.07[a]
Total weight of kidney (g)	0.91±0.08[a]	0.87±0.14[a]	1.09±0.16[a]	0.85±0.10[a]	0.99±0.14[a]
Weight of heart (g)	0.44±0.06[a]	0.40±0.03[a]	0.48±0.10[a,b]	0.39±0.05[a]	0.56±0.07[b]

Values are means ± SD. [a–d]Means with different superscripts along the column are significantly different ($P < 0.05$).

Table 3. Effect of *Irvingia gabonensis* on Biomarkers of kidney function in $KBrO_3$ treated rats

Parameters	Control	$KBrO_3$only (50 mg/kg)	IGonly (1000 mg/kg)	$KBrO_3$(50 mg/kg)+IG (500 mg/kg)	$KBrO_3$only (50 mg/kg)+IG (1000 mg/kg)
Urea (mg/dl)	16.77±1.01[a]	36.85±4.22[c]	18.24±0.78[a]	27.57±2.52[b]	23.48±1.23[b]
Creatinine (mg/dl)	0.77±0.05[a]	1.48±0.12[c]	0.78±0.04[a]	1.14±0.09[b]	1.03±0.07[b]
Uric acid (mg/dl)	4.52±0.06[a]	7.57±0.23[c]	4.61±0.27[a]	5.63±0.06[b]	5.44±0.24[b]
Na^+ (mEq/L)	128.70±2.46[a]	138.63±3.20[c]	128.57±1.61[a]	132.97±1.39[b]	131.70±1.80[a,b]
K^+ (mEq/L)	4.41±0.13[a]	4.36±0.06[a]	4.40±0.11[a]	4.31±0.07[a]	4.33±0.12[a]
Cl^- (mEq/L)	88.63±2.48[a]	97.20±1.55[c]	87.73±2.62[a]	93.23±2.03[b]	94.00±1.06[b,c]
HCO_3^- (mEq/L)	20.10±0.30[b,c]	20.57±0.31[c]	19.50±0.20[a]	19.83±0.35[a,b]	19.83±0.25[a,b]

Values are means ± SD. [a–d]Means with different superscripts along the column are significantly different ($P < 0.05$).

Table 3 shows the assessment of serum biomarkers of kidney function i.e. concentration of urea, creatinine, uric acid and electrolytes i.e sodium, potassium, chloride and bicarbonate indicate the functional integrity of the kidneys. $KBrO_3$ administration significantly ($P<0.01$) increased the level of urea, creatinine, uric acid and electrolytes as compared to control group and group administered IG only. Serum level of these parameters were significantly ($P<0.01$) decreased by administration of IG at both doses (500 mg/kg body weight and 1000 mg /kg body weight) as compared to $KBrO_3$only treated rats. However, more restoration effects on studied parameters were determined at the higher dose (1000mg/kg) of IG. These parameters statistically ($P>0.05$) remained unchanged with the treatment of IG (1000 mg/kg bw) alone as compared to the control group of rat.

Table 4: Qualitative phytochemicals analysis of leaf of *Irvingia gabonensis.*

Phytochemicals	Qualitative results
Saponins	++
Flavonoids	++
Terpenoids	+
Tannins	+
Alkaloids	+++
Phenolics	++
Steroids	+
Cardiac glycosides	+

Table 5: Quantitative Phytochemical composition of leaf of *Irvingia gabonensis*

Phytochemicals	Quantitative availability (mg/100g)
Saponins	23.56±1.01
Flavonoids	36.98±1.04
Terpenoids	5.16±1.22
Tannins	13.61±0.50
Alkaloids	44.27±0.96
Phenols	28.84±0.74
Steroids	6.98±0.19
Cardiac glycosides	5.15±0.17

Values are presented as mean ± standard deviation (n = 3).

Quantitative phytochemical screening revealed the hightest occurance of Alkaloids followed by Flavonoids and Phenols

Effect of ethanol leaf extract of *Irvingia gabonensis* on some antioxidant parameters of $KBrO_3$ treated rats.

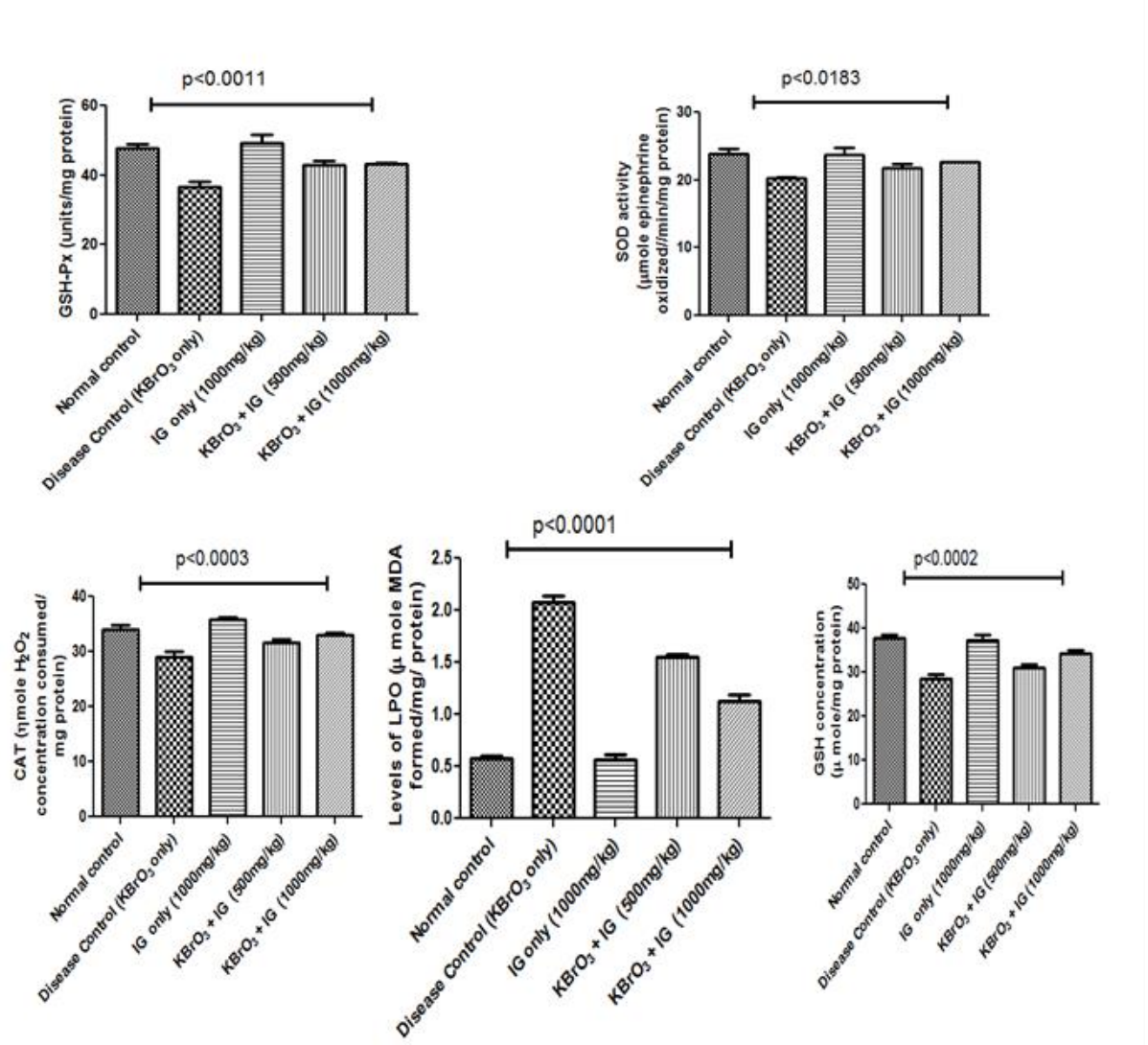

FIG 1. Effect of IG on Kidney antioxidant parameters of $KBrO_3$ treated rats

Irvingia gabonensis enhanced antioxidant status and inhibited oxidative damage in $KBrO_3$-treated rats.The effects of IG on antioxidant status and biomarkers of oxidative stress in the kidney of $KBrO_3$-treated rats are illustrated in Figs. 1. Compared with the control; activities of various antioxidant enzymes such as SOD, CAT, GSH-Px, and the GSH level, were markedly ($p < 0.05$) lower whereas the levels of MDA produced were significantly higher in kidney of rats administered $KBrO_3$ alone. On the other hand, the co-administration of IG at both 500 mg/kg and 1000mg/kg significantly enhanced the activities of these enzymes. Correspondingly, the levels of MDA in the kidney of IG co-treated rats were significantly ($p < 0.05$) lower in comparison with rats exposed to $KBrO_3$ alone.

Effect of ethanol leaf extract of *Irvingia gabonensis* on Liver function parameters of $KBrO_3$ treated rats.

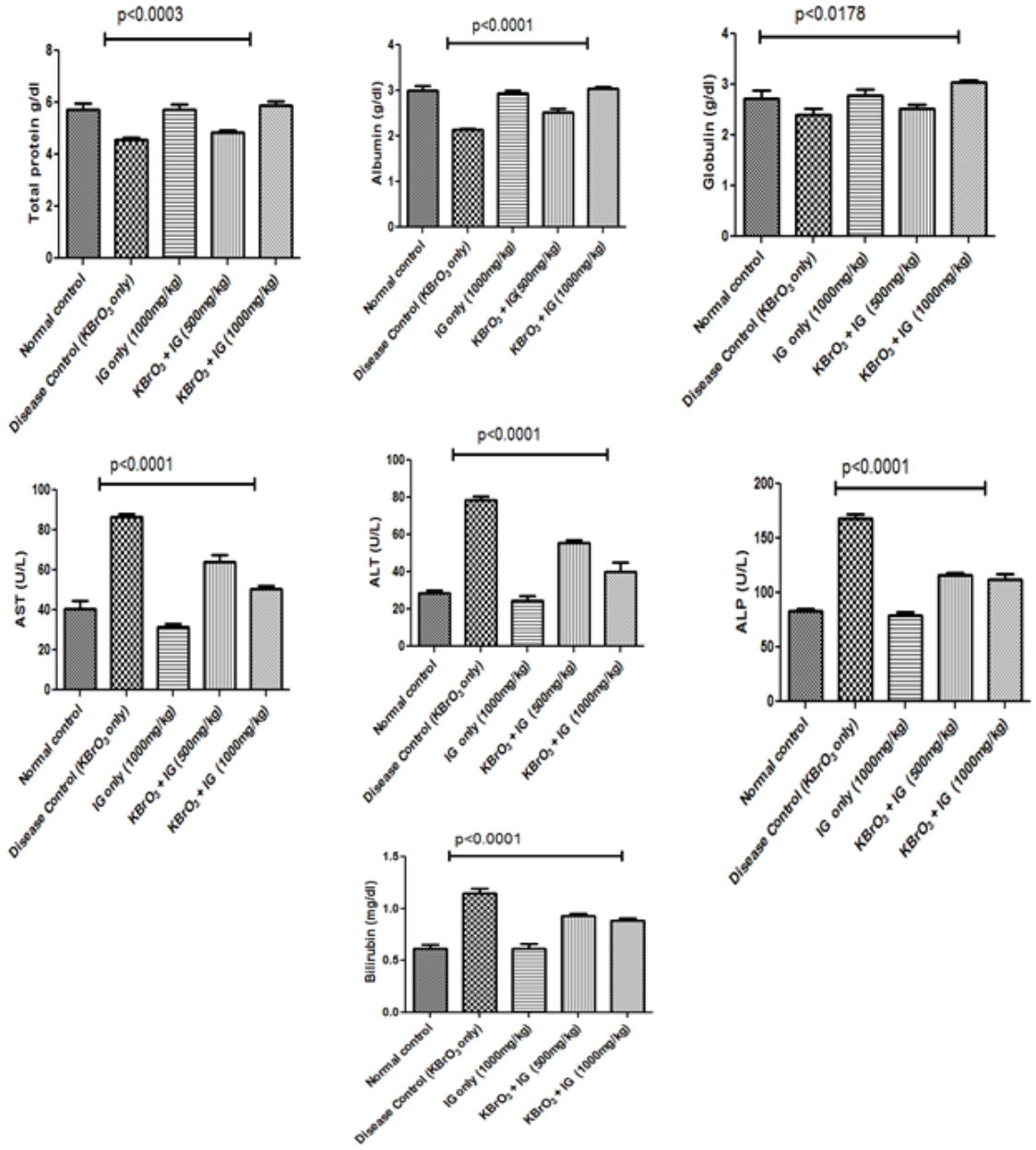

FIG 2 . Effect of IG on liver function parameters of $KBrO_3$ treated rats

Irvingia gabonensis prevented enhanced hepatic function bio-markers in $KBrO_3$-exposed rats. The influence of IG on hepatic function assays in $KBrO_3$ -exposed rats are illustrated in Fig. 2. In comparison with the control, the serum activities of ALT, AST, ALP and Bilirubin were significantly ($P < 0.05$) higher in $KBrO_3$-only exposed rats. Conversely, the administration of IG at both 500 mg/kg and 1000 resulted to a noticeable lower level of liver function tests indistinguishable to control values. $KBrO_3$ administration significantly ($P<0.05$) decreased the total protein, albumin and globulin as compared to control group. Serum level of these parameters were significantly ($P<0.05$) improved by administration of IG as compared to $KBrO_3$ only treated rats. However, more restoration effects on studied parameters were determined at the higher dose (1000 mg/kg) of IG. These parameters were statistically ($P>0.05$) remained unchanged with the treatment of IG (1000 mg/kg) alone as compared to the control.

Effect of ethanol leaf extract of *Irvingia gabonensis* on some Inflammatory biomarkers of $KBrO_3$ treated rats.

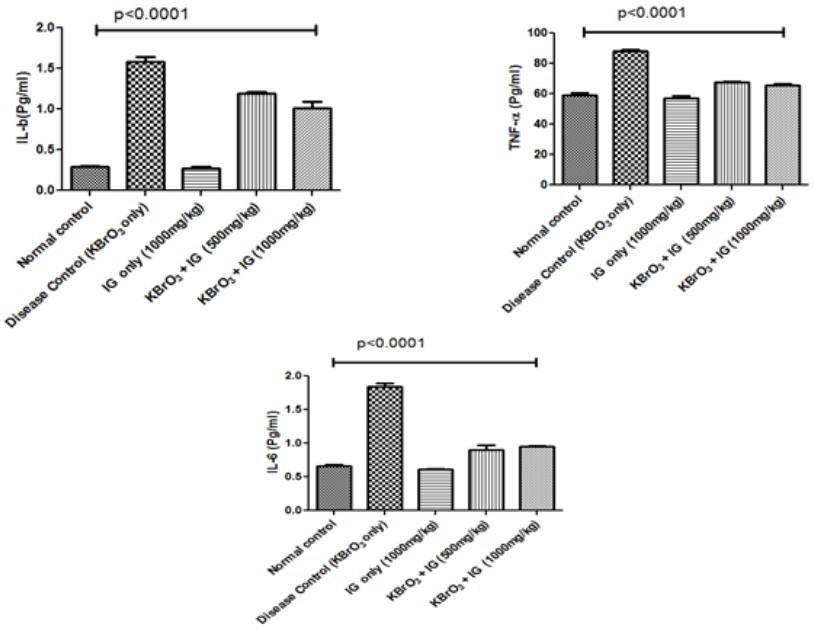

FIG 3. Effect of IG on Inflammatory markers of $KBrO_3$ treated rat

Irvingia gabonensis lowered serum inflammatory mediators in $KBrO_3$-exposed rats.The influence of IG treatment on inflammatory biomarkers in kBrO3-exposed rats are shown in Fig. 3. In comparison with the control, $kBrO_3$ -alone treated elicited significantly ($p < 0.05$) higher IL-b, IL-6 and TNF-α levels in serum of rats. Conversely, the IG co-treatment at both 500 mg/kg and 1000mg/kg elicited a significant ($p < 0.05$) lower levels of these inflammatory biomarkers.

Effect of ethanol leaf extract of *Irvingia gabonensis* on Lipid profile of $KBrO_3$ treated rats.

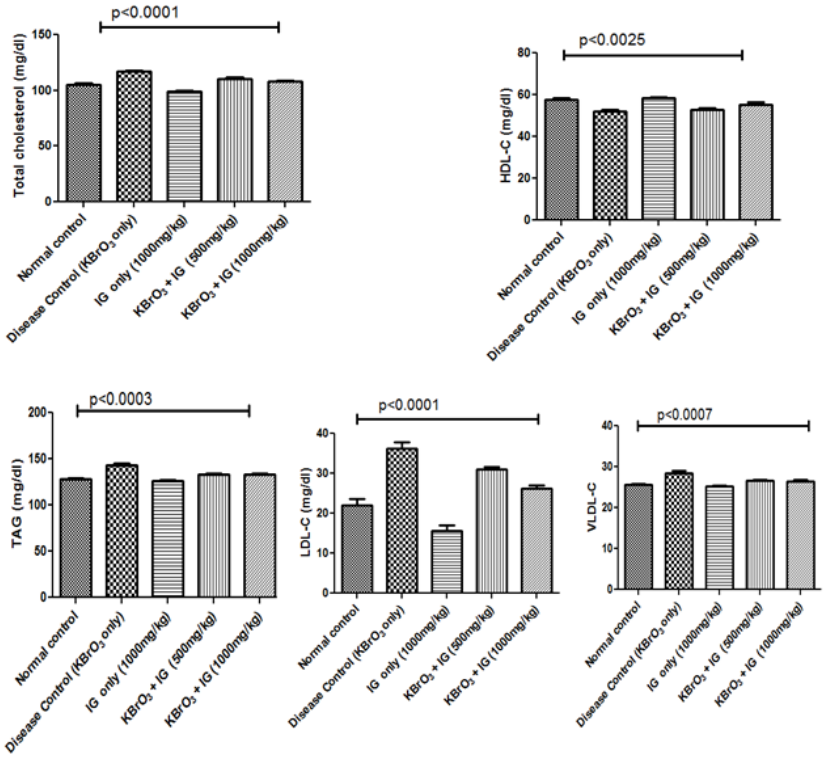

FIG 4. Effect of IG on lipid profile parameters of $KBrO_3$ treated rats

Lipid profile in the sera

Fig 4.shows the lipid profile in the sera of the rats that were studied. As shown in the Fig 4, there were significant increases ($p<0.05$) in the total cholesterol, TAG, LDL and VLDL but significant decreases ($p<0.05$) in the HDL concentrations of the $KBrO_3$ only group in comparison with the control. On the other hand, there were significant decreases ($p<0.05$) in the total cholesterol, TAG, LDL and VLDL but significant increases ($p<0.05$) in the HDL concentrations of IG alone 1000mg and both doses of IG (500mg/kg and 1000mg/kg) as compared to the $KBrO_3$ only group.

Effect of ethanol leaf extract of *Irvingia gabonensis* on histological changes of kidneys of $KBrO_3$ treated rats.

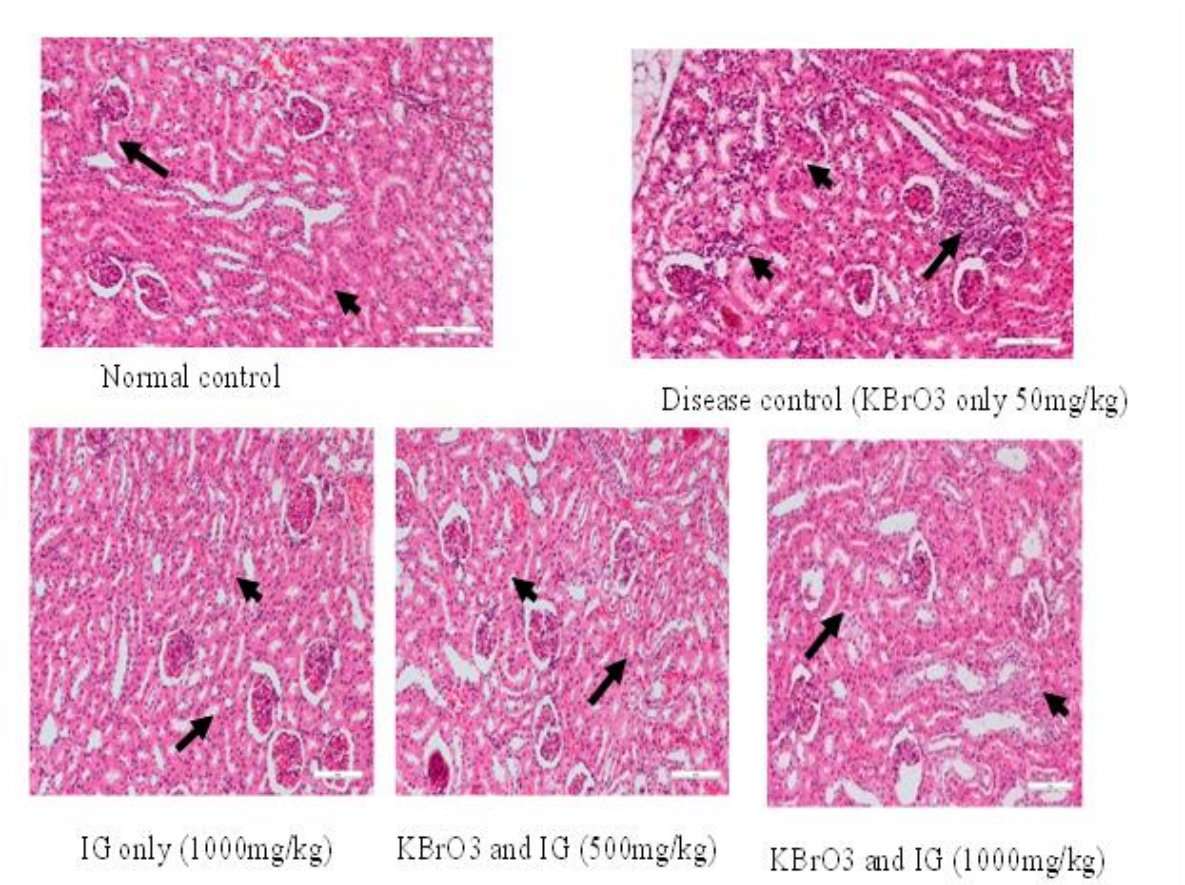

Fig 5. Effect of IG on Histology of the Kidneys of $KBrO_3$ treated rat

The histological changes in the kidneys are presented in Fig 5 above. The sections of control group showed normal histology including normal glomerulus, bowman capsule, distal and proximal convoluted tubules. Marked histological changes were observed in cortex of kidneys in $KBrO_3$-treated rats. The cross section showed tubular degeneration, tubular congestion, tubular dilatation and glomerular injuries in $KBrO_3$-treated rats. Treatment of IG to $KBrO_3$ treated rats markedly recovered the toxic changes near to the control rat. Histology of the kidneys showed normal glomerulus, bowman capsule, reversed the tubular degeneration, congestion and dilatation and prevented interstitial edema and capillary congestion in a dose dependent way. However, treatment of IG (1000 mg/kg) alone did not induce histopathological changes in kidneys.

Effect of ethanol leaf extract of *Irvingia gabonensis* on histological changes of the Liver of $KBrO_3$ treated rats.

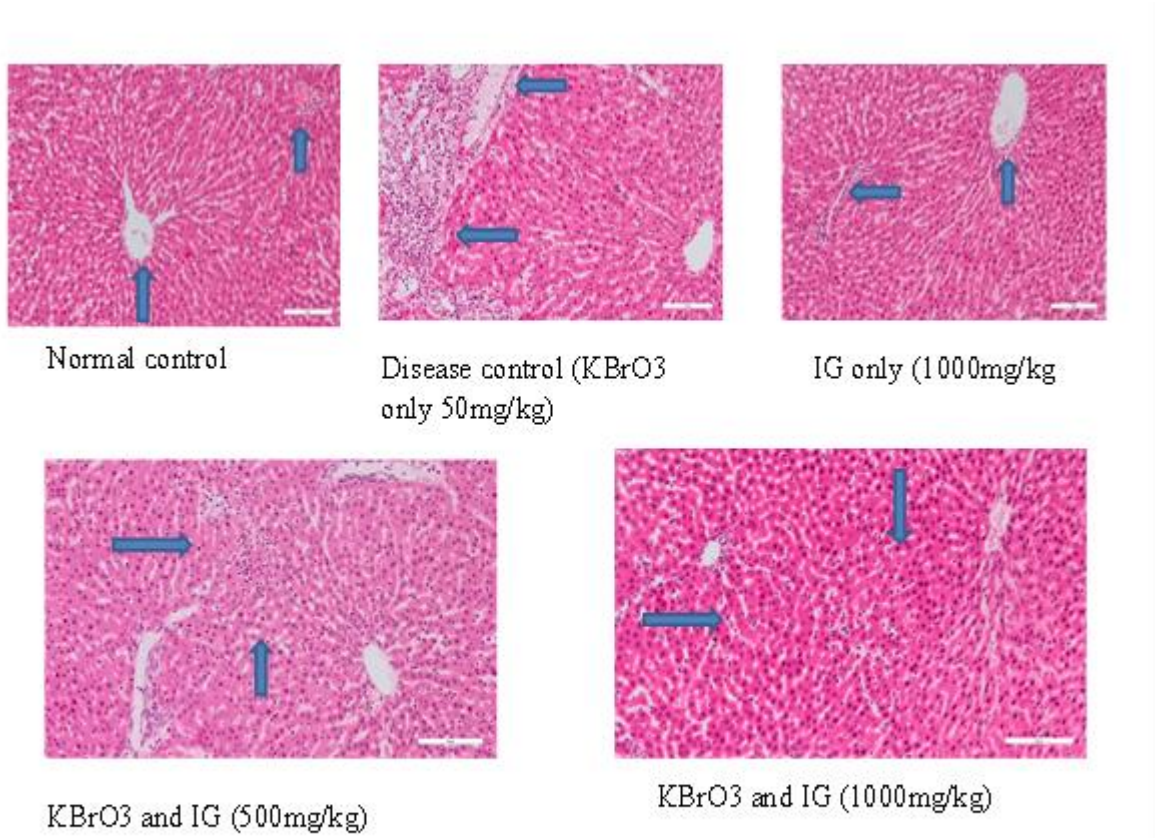

Fig 6. Effect of IG on Histology of the Liver of $KBrO_3$ treated rat

The histological changes in the liver tissues are presented in Fig 6 above. The sections of control group showed normal histomorpholgy including normal hepatocytes arranged in interconnecting cords around the central veins were observed. Severe necrosis with moderate to marked infiltration of inflammatory leukocytes were observed in the hepatocytes of rats treated with $KBrO_3$ only. Treatment of IG 500mg/kg to $KBrO_3$ treated rats showed mild multifocal areas of leukocytic inftration while treatment of IG 1000mg/kg to $KBrO_3$ treated rats also showed mild of individual hepatocellular necrosis with mild leukocytic inftration However, treatment of IG(1000 mg/kg) alone did not induce histopathological changes in the liver, normal hepatic histomorphology were observed .

IV. Discussion

The current study disclosed, for the first time, the valuable health effect of *Irvingia gabonensis* against $KBrO_3$ induced nephrone toxicity. In this study, we examined the chemopreventive efficacy of *Irvingia gabonensis* against $KBrO_3$-induced renal oxidative stress and toxicity in male Wistar rats. Animals treated with $KBrO_3$ alone exhibited a marked decrease in the body weight gain consequently indicating general toxicity and disturbance of metabolic functions in the exposed rats. The restoration of the body weights gain following co-treatment with *Irvingia gabonensis* at both doses demonstrated the beneficial effects of *Irvingia gabonensis* on the metabolism in the experimental animals. Similar alterations for body weight with KBrO3 administration have been determined previously (Cadenas and Barja, 1999, Sai *et al.*, 1992). Organ weight can be the most sensitive indicator of the effect of toxicity as significant differences in organ weights between treated and control animals may occur in the absence of any morphological changes or may precede morphological changes (Ying *et al.*, 2013). The relative kidney, heart and liver weights of the disease control or normal rats administered *Irvingia gabonensis* were statistically the same with that of the normal control. Similarly, the relative kidney,heart and liver weights of the $KBrO_3$ treated rats administered *Irvingia gabonensis* (at both doses) were statistically the same with that of the disease control. These findings suggest the non-toxicity of *Irvingia gabonensis* to the kidney,heart and liver. Similar reports were given by Devkota *et al.*, (2022). In the

present study, the observations made with respect to percent increase in body weight, relative kidney, heart and liver weight in male rats appeared to suggest that *Irvingia gabonensis* can alleviate $KBrO_3$ induced toxicity in these animals.

During kidney function impairment, there is increase in blood levels of creatinine (generated from muscle metabolism) urea and uric acid increase due to poor clearance by the kidney (Okechukwu *et al.,* 2013). High levels of urea, creatinine, uric acid and the electrolytes (Na^+,K^+ , Cl^- and $HCO3^-$) in serum as observed in the experiment reflect the kidney dysfunction and renal injuries induced by $KBrO_3$ treatment (Ozturk *et al.,* 2003). *Irvingia gabonensis* administration to rats treated with $KBrO_3$ ameliorated the toxicity of $KBrO_3$ in kidneys and restore the level of the studied parameters in a concentration dependent manner. These results suggest that *Irvingia gabonensis* can be used as Nephrone protective agent against KBrO3 induced toxicity, and collaborates with the finding of Muhammad *et al.,* 2021 that reported curative roles of *Irvingia gabonensis* in acetaminophen induced nephrotoxicity.

Usually, antioxidant defense mechanisms protect cellular macromolecules from the damaging effect of ROS, such as hydroxyl radical, superoxide anion, and peroxides,that have direct link with oxidative damage of kidney (Ebokaiwe *et al.,* 2019). We observed that animals exposed to KBrO3 alone showed a marked lower GSH level and activities of antioxidant enzymes such as SOD, CAT, GST, and GSH-Px. This observation indicates insufficiency in the levels of antioxidants needed to sift harmful free radicals and prevent the induction of oxidative stress in the kidney tissues. The high levels of LPO in the tissues of animals exposed to $KBrO_3$ alone demonstrated that $KBrO_3$ elicited ROS/RONS production that overwhelms the antioxidant competence, which consequently led to oxidative damage in the kidney of the $KBrO_3$ alone treated animals. Conversely, the decreased MDA levels with the concurrent improvement in the antioxidant status following co-treatment with *Irvingia gabonensis* at both doses is attributed to the antioxidant and anti-lipid peroxidative activities of which is vital in placating oxidative damage in the treated animals.

KBrO3 alone-treated animals, in the current study showed significant elevation of liver function indices in the serum. This is an indication of liver injury since their leakage into serum defines the severity of damage (Hamsa and Kuttan, 2011). Hepatic tissues were the primary sites for the microsomal activation of the drugs. Hence hepatic metabolism of $KBrO_3$ elicited formation of toxic metabolite that compromised the architecture of the liver tissues as demonstrated by elevated liver enzymes and Bilirubin in the serum. The decrease activities of serum AST, ALT and ALP and lower levels of Bilirubin in animals co-dosed with *Irvingia gabonensis* at both doses demonstrate the protective activity of *Irvingia gabonensis* against $KBrO_3$-induced liver injury. Thus, *Irvingia gabonensis* prevents $KBrO_3$-induced liver injury via attenuation of oxidative-inflammatory stress and restoration of antioxidant defenses.

The present study revealed that KBrO3 administration caused marked reduced levels of serum albumin, globulin and protein in KBrO3 only-treated rats which might have resulted from considerable leakage due to injuries to glomeruli and tubules. The results suggested that *Irvingia gabonensis* prevented $KBrO_3$-induced toxicity, by increases in the levels of serum albumin, globulin and protein in animals co-dosed with *Irvingia gabonensis* at both doses compared to the disease control. Studies have shown that different plant extracts can significantly reduce the renal injuries induced through KBrO3 intoxication treatment (Ozturk *et al,* 2003, Adewole *et al.,* 2007).

The current study further accentuates induction of inflammatory response following $KBrO_3$ treatment via an increase in the inflammatory cytokines IL-b,TNF-α and IL-6, suggesting chronic inflammatory condition in the kidneys of the disease control group of rats. Tumor necrosis factor-α is a pro-inflammatory cytokine that is mainly secreted by macrophages and it plays a vital role in initiating the inflammatory response and increasing oxidative stress in tissues (Eleazu *et al.,* 2020) *Irvingia gabonensis* co-treatment inhibited oxidative stress and lowered the proinflammatory cytokines thereby preventing $KBrO_3$-induced injury in the kidney. Current finding therefore adduces a scientific rationale for the traditional usage of *Irvingia gabonensis* as an anti-inflammatory agent

Dyslipidemia refers to an elevation in blood concentrations of total cholesterol or LDL or decreased concentrations of HDL (Fodor, 2011). In this study, we found increased concentrations of cholesterol, TAG, LDL, VDL but decreased HDL concentration in the sera of the disease control group, establishing the development of dyslipidaemia in this group of rats. Although how dyslipidaemia leads to BPH has not been fully elucidated, attenuation of TAG, total cholesterol, LDL, VLDL, with corresponding increase in HDL in the *Irvingia gabonensis* co-treatment groups suggest the capacity of to *Irvingia gabonensis* ameliorate dyslipidaemia.

Histopathological changes can alter the capacity of tubular absorption, thus bringing about functional overload of nephrons with subsequent renal dysfunction (Khan *et al.,* 2010, Adewole *et al.,* 2007). Renal dysfunction induced by $KBrO_3$ as observed in this experiment is characterized by marked histological changes in cortex of kidneys in KBrO3-treated rats. The cross section showed tubular degeneration, tubular congestion, tubular dilatation and glomerular injuries in $KBrO_3$-treated rats. This study corroborates earlier reports by Dio *et*

al., 1991 and Bhattcharya *et al.,* 2005 on histopathological changes induced by $KBrO_3$ in experimental animals. Treatment of *Irvingia gabonensis* to $KBrO_3$ treated rats markedly recovered the toxic changes near to the control rat. Histology of the kidneys showed normal glomerulus, bowman capsule, reversed the tubular degeneration, congestion and dilatation and prevented interstitial edema and capillary congestion in a dose dependent way. These histological alterations abated by *Irvingia gabonensis* co-treatment could be predicated on its anti-oxidant, anti-inflammatory, and anti-lipid peroxidation activities, hence protecting against tissue damage. This was further confirmed by the histology result of the liver architecture, which demonstrated severe necrosis with moderate to marked infiltration of inflammatory leukocytes were observed in the hepatocytes of rats treated with $KBrO_3$ only while treatment of *Irvingia gabonensis* 500mg/kg to $KBrO_3$ treated rats showed mild multifocal areas of leukocytic inftration while treatment of *Irvingia gabonensis* 1000mg/kg to $KBrO_3$ treated rats also showed mild of individual hepatocellular necrosis with mild leukocytic inftration. However, treatment of *Irvingia gabonensis* (1000 mg/kg) alone did not induce histopathological changes in the liver, normal hepatic histomorphology were observed. This findings further underscores the role of *Irvingia gabonensis* in attenuating hepatic-renal toxicity associated with $KBrO_3$ exposure.

In conclusion, our study indicates that $KBrO_3$ exposure enhances renal and hepatic toxicity by aggravating the depletion of antioxidant enzymes, induces inflammation, dyslipidemia and and tissue damage as shown in the histology features. However, *Irvingia gabonensis* abated the altered parameters due to its biological activities, such as antioxidant and anti-inflammatory properties, as well as its ability to attenuate lipid peroxidation and capacity to ameliorate the $KBrO_3$ induced toxicity. This study substantiated the scientific evidence in favors of *Irvingia gabonensis* pharmacological use in renal injuries.

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