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Deleterious effects of Potassium bromate administration on renal and hepatic tissues of Swiss Mice

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Abstract

Potassium bromate ($KBrO_3$) is widely used as a food additive and is a major water disinfection by-product. The present study reports the side effects of $KBrO_3$ administration in Swiss mice. Animals were randomly divided into three groups: control, low dose $KBrO_3$ (100 mg/kg/day) and high dose $KBrO_3$ (200 mg/kg/day) groups. Administration of $KBrO_3$ led to decreased white blood corpuscles (WBCs), red blood corpuscles (RBCs) and platelets count in the animals of both the high and the low dose groups. Altered lipid profile represented as low density lipoprotein (LDL), high density lipoprotein (HDL) and cholesterol levels were observed in plasma samples of both $KBrO_3$ treated groups of mice. Also, an increased plasma level of LDH was detected in both $KBrO_3$ treated groups. Histological investigations showed impaired renal and hepatic histology that was concomitant with increased plasma Creatinine level in both of $KBrO_3$-treated groups. Nevertheless, decreased glutathione (GSH) level in both renal and hepatic tissue of mice after $KBrO_3$ intake was detected. These results show that $KBrO_3$ has serious damaging effects and therefore, its use should be avoided.

Keywords: Platelets, Lipid profile, LDH, Creatinine, Reduced glutathione

1. Introduction

Potassium bromate ($KBrO_3$) is a well-known flour improver that acts as a maturing agent (Vadlamani and Seib, 1999). It has been in use as a food additive for the past 90 years (Oloyede and Sunmonu, 2009). It acts principally in the late dough stage giving strength and elasticity to the dough during the baking process while also promoting the rise of bread. $KBrO_3$ is also used in beer making, cheese production and is commonly added to fish paste products (Ahmad and Mahmood, 2014). Additionally, it is used in pharmaceutical and cosmotic industries and is a constituent of cold wave hair solutions (Oloyede and Sunmonu, 2009). Moreover, $KBrO_3$ can appear as a byproduct in an ozonization of water containing bromide. As a result of $KBrO_3$ biotransformation, free radicals generation can cause oxidative damage to essential cellular macromolecules, leading to marked nephrotoxicity and cancer in experimental animals (Chipman et al., 1998). International Agency for Research on Cancer (IARC) has classified $KBrO_3$ as a possible human carcinogen (group 2B) (IARC, 1999) and its application in food processing was restricted. Indeed, many previous reports has documented that $KBrO_3$ can induce multiple organ toxicity in humans and experimental animals (Farombi et al., 2002; Kujawska et al., 2013; Ahmad et al., 2015) and that kidney is considered to be the primary target organ of these dangerous compound (Kurokawa et al., 1990; Ahmad et al., 2013). $KBrO_3$ is extremely irritating and injurious to tissues especially those of the central nervous system (CNS) and kidneys. The pathological findings included renal tissue damage and haemolysis (Robert and William, 1996). Carcinogenic and mutagenic effects of $KBrO_3$ have been also reported in experimental animals (Kurokawa et al., 1987). Several cases of accidental poisoning in children resulting from ingestion of

bromate solution and sugar contaminated with bromate were reported as the source of an outbreak of mild poisoning in New Zealand (Paul, 1966). Consequently, $KBrO_3$ has been banned in several countries including the United Kingdom in 1990, Nigeria in 1993 and Canada in 1994 (Oloyede and Sunmonu, 2009). Toxicological studies have convincingly shown that $KBrO_3$ affects the nutritional quality of bread as the main vitamins available in bread are degraded (Sai et al., 1992). Oral doses of 185–385 mg/kg body weight results in irreversible toxic effects like renal failure and deafness in humans while lower doses are accompanied with vomiting, diarrhea, nausea and abdominal pain (Mark, 1988). It is known that $KBrO_3$ induces oxidative stress in tissues (Sai et al., 1991; Watanabe et al., 1992; Parsons and Chipman, 1992, 2000) that could be the basis of bromate-induced carcinogenesis (Chipman et al., 2006). The present study attempts to assess the effects of oral administration of $KBrO_3$ on the lipid profile in plasma, oxidative stress, hepatic and renal histomorphology of Swiss mice using two different doses of $KBrO_3$ to compare their effects.

2. Materials and Methods

2.1. Animals

Forty five (45) Swiss Webster (SW) mice were obtained from animal house- College of pharmacy- king Saud University and maintained and monitored in a specific pathogen-free environment. All animal procedures were performed in accordance with the standards set forth in the Guidelines for the Care and Use of Experimental Animals issued by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The study protocol was approved by the Animal Ethics Committee at King Saud University. All animals were allowed to acclimatize in plastic cages inside a well-ventilated room for one week prior to the experiment. The animals were maintained under standard laboratory conditions (temperature of 23°C, relative humidity of 60–70% and a 12-hour light/dark cycle), fed a diet of standard commercial pellets and given water *ad libitum*.

2.2.$KBrO_3$ Preparation and dosing schedule

Potassium bromate salt, a product of British drug home limited, Poole England was supplied in its white crystalline form by ASILA chemicals (Saudi Arabia). It was then dissolved in water to prepare the 100 mg/kg dose (0.5 gm/L) and the 200 mg/kg dose (1 gm/L). Animals were divided into 3 groups as follows: Group (I) control group (was given distilled water); Group (II) Low dose $KBrO_3$ group (was given 100 mg/kg); Group (III) High dose $KBrO_3$ group (was given 200 mg/kg). $KBro_3$ was orally administered daily through oral intubation at the two doses of 100 and 200 mg/kg/day for 42 days.

2.3.Sample collection

Blood was collected from the heart in heparinized tubes and plasma was obtained for biochemical investigations. Plasma was stored at −80°C until use. Small pieces of liver and kidneys were removed, cut and put in sterile saline. The pieces were then fixed in 10% neutral buffered formalin and then embedded in paraffin.

2.4.Histological analysis of hepatic and renal tissues

The preparation of tissues for histological examination was done as described by Krause (2001); the photomicrographs were observed using the Leitz, DIALUX research microscope at x200.Pathological evaluation in H/E stained tissue sections was done by a pathologist blinded for the experimental regimen.

2.5.Cell Blood Count (CBC)

Whole blood samples were analyzed with an automatic Vet abc™ Animal Blood Counter (Horiba ABX, Montpellier, France) using the hematology kits specified for that instrument (Horiba ABX, France) according to the manufacturer's instructions.

2.6.Determination of Creatinine level in plasma

Plasma samples were analyzed using commercial kits (bioMerieux, Marcy I'Etoile, France) for Creatinine according to the instructions of the manufacturer. Absorbance was measured with an Ultrospec 2000 U/V spectrophotometer (Amersham Pharmacia Biotech, Cambridge, England).

2.7.Lactate dehydrogenase (LDH)

Lactate dehydrogenase was determined using specified kits LiquiUV Test (Human, Germany) according to the manufacturer's instructions. Briefly, 20 µl of plasma was added to 1000 µl buffer solution (provided by in the kit) then incubated in cuvettes for 5

minutes at 30º C. After that, 250 µl of the substrate was mixed with the solution and the absorbance was monitored after 1, 2 and 3 minutes. The colour development was detected at 340 nm in a spectrophotometer.

2.8.Lipid Profile in Plasma

LDL, HDL and total cholesterol levels were measured by an enzymatic colorimetric kit (Wako Chemicals USA, Inc.). Briefly, 10 µl of plasma were put into tubes and 1 ml of colour reagent solution was then added. 10 µl of standard solution (provided by in the kit), were put into tubes and 1 ml of colour reagent solution was then added. The solution was mixed well and incubated at 37°C for 5 min. The colour development was detected at 500 nm in a spectrophotometer.

2.9.Glutathione (GSH) assay

Glutathione content was determined according to the procedure of Beutler *et al*. (1963) with some modification. Briefly, 0.20 ml of tissue supernatant was mixed with 1.5 ml precipitating solution containing 1.67% glacial metaphosphoric acid, 0.20% Na-EDTA and 30% NaCl. The mixture was allowed to stand for 5 min at room temperature and centrifuged 1,000 *g* for 5 min. One ml clear supernatant was mixed with 4 ml 0.30 M Na_2HPO_4 and 0.50 ml DTNB reagent (40 mg 5, 5'dithiobis-(2-nitrobenzoic acid dissolved in 1% sodium citrate). A blank was similarly prepared in which 0.20 ml water was used instead of the brain supernatant. The absorbance of the color was measure at 412 nm in a spectrophotometer.

2.10. Statistical analysis

Prior to further statistical analysis, the data were tested for normality using the Anderson-Darling test, as well as for homogeneity variances. The data was normally distributed and

is expressed as the mean ± standard error of the mean (SEM). Significant differences among the groups were analysed by one- or two-way ANOVA followed by Bonferroni's test for multiple comparisons using PRISM statistical software (GraphPad Software). The data was also reanalysed by one- or two-way ANOVA followed by Tukey's post-test using SPSS software, version 17. Differences were considered statistically significant at $P<0.05$.

3. Results

3.1.Decreased WBCs, RBCs and platelets count after $KBrO_3$ intake

WBCs count was significantly decreased in both of $KBrO_3$ treated groups. As shown in table 1, the low dose of $KBrO_3$ was associated with a lower number of WBCs in comparison to the control group. Additionally, the high dose of $KBrO_3$ was accompanied with a much more decrease in the WBCs count in comparison to either the control or the low dose group. RBCs count was also decreased in the low dose $KBrO_3$ group in comparison to the control group. Similarly, the decrease in RBCs count was higher in the high dose $KBrO_3$ group in comparison to both the low dose and the control one. Platelets count was having a similar pattern of decrease in both of $KBrO_3$ treated groups. A significantly decreased Platelets count was detected in the low dose $KBrO_3$ group. On the other hand, the high dose $KBrO_3$ group has showed a lower platelets count in comparison to either the control group or the low dose $KBrO_3$ group.

3.2.Altered lipid profile in plasma of $KBrO_3$ treated mice

Disturbance in lipid profile in plasma is considered as an indicator for many physiological disorders. LDL, HDL and cholesterol levels in plasma samples of the three experimental groups were investigated. Both of the low and the high doses of $KBrO_3$ were accompanied with a significant reduction in the plasma concentrations of HDL (Figure 1a). Conversely, the plasma level of LDL was increased in both of the low and the high dose $KBrO_3$ groups. A significant increase was detected in the high dose $KBrO_3$ group in comparison to the control group (Figure 1b). Nevertheless, the change in the plasma level of cholesterol (Figure 1c) in both of $KBrO_3$ groups was not significant in comparison to the control group.

3.3.$KBrO_3$ treatment was associated with an increased plasma level of LDH

LDH is often used as a marker of tissue breakdown and can function as an indicator for liver toxicity. Figure 2 illustrates that both groups of the high and the low doses of potassium bromate were associated with a significant increase in the plasma level of LDH in comparison to the control group. However, the high dose of potassium bromate was accompanied with a much more increase in the LDH level in comparison to either the control or the low dose group.

3.4.Impaired hepatic and renal histology concomitant with increased plasma Creatinine in both $KBrO_3$ groups

As a result of $KBrO_3$ treatment, hepatic tissue sections of $KBrO_3$ treated mice have showed a congestion of central vein with a relative increase in Kuppfer cells (KCs) in comparison to the control group (Figure3). Renal tissue of $KBrO_3$ treated group of mice was largely affected in comparison to the control group. Hemorrhage was seen in both $KBrO_3$ treated groups. Dilated blood vessels were seen in the high dose $KBrO_3$ treated group (Figure 4). To confirm these findings, Creatinine level in plasma, which is considered as an important indicator for kidney function, was determined. As illustrated in figure 5, a significant increase in the plasma level of Creatinine in both of $KBrO_3$ treated groups was detected. The low dose group had a higher plasma level of Creatinine in comparison to the control. The high dose group has exhibited a much more increase in the plasma level of Creatinine in comparison to both the control and the low dose one.

3.5.Decreased glutathione level in both renal and hepatic tissues of $KBrO_3$ treated mice.

Reduced glutathione (GSH) is an important antioxidant that plays a crucial role in nearly all living organisms. $KBrO_3$ treatment had a negative impact on both the renal and the hepatic level of this important molecule. In the low dose $KBrO_3$ group, both of the renal and the hepatic levels of GSH were significantly decreased in comparison to that of the control group. At the same time,

a significant reduction in the level of this crucial molecule was also monitored in both the renal and hepatic homogenates of the high dose $KBrO_3$ group in comparison to either the control group or the low dose $KBrO_3$ group (Figure 6).

4. Discussion

Potassium bromate ($KBrO_3$) is widely used as improving additive for bread making (Ahmad et al., 2015) and marketed as a neutralizer in home permanent cold wave hair kits that caused several cases of accidental poisoning in children resulting from the ingestion of this solution (Paul, 1966). Due to its hazardous effects, it has been forbidden in various countries (Oloyede and Sunmonu, 2009). Toxicity studies in animals are commonly used to assess potential health risk in humans caused by intrinsic adverse effects of chemical compounds (Kurokawa et al., 1990). These adverse effects may manifest significant alterations in the levels of bio molecules, normal functioning and histomorphology of the organs (Ahmad et al., 2014). The current study was designed to investigate some of the biochemical changes induced by $KBrO_3$ intake in Swiss Mice. We have observed that the total reticulocyte, leukocyte and platelet counts in the plasma samples of both $KBrO_3$ treated groups have been significantly decreased in comparison to the control group. These reductions in the leukocyte and platelet counts could be due to the DNA strand breakage in these cells induced by the oxidative stress associated with $KBrO_3$, (Chipman et al. 1998, Sai et al.2000, Parson and Chipman, 2000, Thompson and Westfall 1949). Furthermore, there could have been bone marrow suppression with selective megakaryocytic depression (Hoffbrand et al.2004). So, the reductions in the RBCs, WBCs and platelets could imply selective systemic toxicity effect by $KBrO_3$. Lipid profile represents an important indicator of several pathological conditions. The most common metabolic contributor to the coronary artery disease is the atherogenic lipoprotein profile, characterized by an increased LDL level and a deficiency of HDL level (Superko et al., 2002). Many studies have reported that increased level of LDL is associated with higher risk of atherosclerosis while elevated level of HDL is linked to reduced occurrences of cardiovascular disorders (Grover-Paez and Zavalza-omez, 2009; Olukanni et al., 2013). In the current study, the level of plasma HDL decreased with both doses of $KBrO_3$ leading to elevated atherogenic index which can be used to predict the risk for development of

cardiovascular disorders. Therefore, the high ratio of LDL to HDL, caused by $KBrO_3$, may implicate increased tendency for the development of atherosclerosis. LDH is considered as a liver toxicity indicator and the increased LDH level in $KBrO_3$ groups that has been observed in the current study is in accordance with previous reports (Ahmad et al., 2014). In another study, $KBrO_3$ induced chromosomal aberrations (CA) and decreased both the cell proliferation index (PI) and the mitotic index (MI) of human peripheral lymphocytes in vitro (Kaya and Topaktaş, 2007). Histological observation of hepatic tissue sections has confirmed the liver pathology due to $KBrO_3$. Previous studies have illustrated that $KBrO_3$ treatment in wister rats have hepatotoxic effects (Oyewo et al., 2013). $KBrO_3$-mediated renal injury in Wistar rats was also recorded before (Khan and Sultana, 2005). In the current study, histological findings in renal tissue of $KBrO_3$ treated groups were supported by previous reports (Kurokawa et al., 1990). A dose-dependent increase in the numbers of eosinophilic droplets within the proximal tubule epithelium was observed in male F344 rats exposed to 20,100, 200, or 400mg/L $KBrO_3$ for 12 weeks (Wolf, 1998). Kurokawa et al. (1987) reported similar lesions in proximal renal tubules of male F344 rats following 13 weeks exposure of 500mg/L $KBrO_3$. In addition to that, Dodd et al (2013) have reported similar results in the same animal model. So the results in the current study agree very well with the results of these sub chronic studies. Elevated levels of Creatinine in plasma were observed confirming previous reports that $KBrO_3$ ingestion causes acute kidney damage (Kurokawa et al., 1990; Bao et al., 2008). Reduced glutathione is an important antioxidant molecule that can be used by many organs, including kidney and liver, to withstand the induced oxidative stress. Previous studies have illustrated that $KBrO_3$ can decrease the tissue content of this molecule (Chipman et al., 1998; Parsons and Chipman, 2000). In agreement with these previous results, the current study illustrated that renal and hepatic levels of GSH have been reduced after $KBrO_3$ treatment with more reduction in the high dose $KBrO_3$ group in comparison to the low dose one. A similar effect has been observed in our previous study in brain tissue

(Ajarem et al., 2016) Taken together, our data reveals that $KBrO_3$ has several harmful effects on the biochemical and histological levels and therefore, its consumption should be prohibited.

5. Conclusions

$KBrO_3$ treatment in Swiss Mice has several consequences like disturbance in blood biochemistry, renal and hepatic histopathology and decreased antioxidant capacity. These dangerous effects should stop its use in human being.

Competing interests:

The authors declare no conflicts of interest. This manuscript has not been published or submitted elsewhere. This work complies with the Ethical Policies of the Journal and has been conducted under internationally accepted ethical standards following relevant ethical review.

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Authors' contributions:

NGA put the design of the experiment and carried out all the lab work, preparing the figures and drafted the manuscript. **JA** participated in the design of the study and helped to draft the manuscript. **AA** participated in the design of the study and helped to draft the manuscript. **SNM** participated in the design of the study, participated in the figures preparation and helped to draft and edit the manuscript. **MAM**

participated in the design of the study, helped to perform the statistical analysis and helped to draft the manuscript.

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Table and Figure legends:

Figure1: Effect of $KBrO_3$ on the lipid profile in plasma samples of treated mice using two different doses of $KBrO_3$. (a) Plasma level of high density lipoprotein, (b) Plasma level of low density lipoprotein, (c) Plasma level of cholesterol. The data are the mean ±SEM for 10 mice per group. $^{*}P<0.05$ for low dose $KBrO_3$ treated group vs. control group; $^{\#}P<0.05$ for high dose $KBrO_3$treated group vs. control group; $^{+}P<0.05$ for high dose $KBrO_3$ treated group vs. low dose $KBrO_3$ treated group.

Figure2: Effect of $KBrO_3$ on the lactate dehydrogenase level in plasma samples of treated mice. The data are the mean ±SEM for 10 mice per group. $^{*}P<0.05$ for low dose $KBrO_3$ treated group vs. control group; $^{\#}P<0.05$ for high dose $KBrO_3$treated group vs.

control group; $^{+}P<0.05$ for high dose $KBrO_3$ treated group vs. low dose $KBrO_3$ treated group.

Figure3: Effect of $KBrO_3$ on the histology of liver. Sections of liver showing central vein (CV), congested central vein (CCV), hepatic sinusoid (S), vacuoles (V), hepatic cell (HC), Kuppfer cell (KC). (A, B) control group, (C, D) potassium bromate100 mg/kg group, (E, F) potassium bromate200 mg/kg group. Scale bar = 400 μm in A, C, E and 50 μm in B, D, F

Figure4: Effect of $KBrO_3$ on the histology of kidney. sections in the kidney showing the kidney tubules (arrow head), Bowman's capsule (arrow),Hemorrhage (H) and dilated blood vessels (DV).(**A**, **B**) control group, (**C**, **D**) potassium bromate100 mg/kg group, (**E**, **F**) potassium bromate200 mg/kg group. (H & E stain, Scale bar = 200 μm in A, C, E and 50 μm in B, D, F)

Figure5: Effect of $KBrO_3$ on the plasma level of Creatinine. The data are the mean ±SEM for 10 mice per group. $^{*}P<0.05$ for low dose $KBrO_3$ treated group vs. control group; $^{\#}P<0.05$ for high dose $KBrO_3$treated group vs. control group; $^{+}P<0.05$ for high dose $KBrO_3$ treated group vs. low dose $KBrO_3$ treated group.

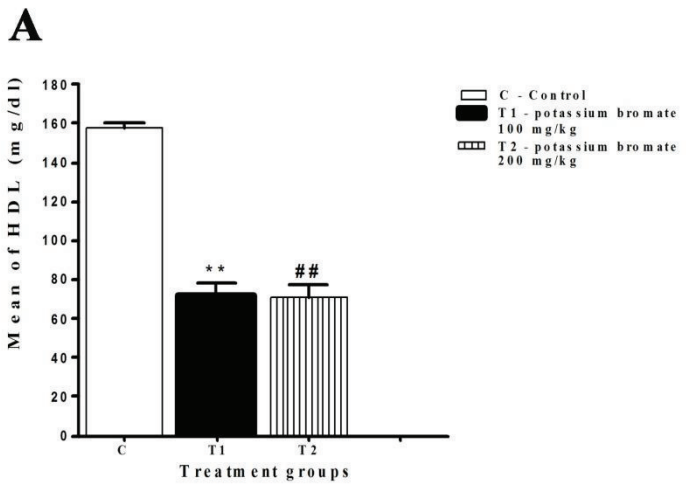
Figure6: Effect of $KBrO_3$ on the hepatic and renal level of GSH. The data are the mean ±SEM for 10 mice per group. $^{*}P<0.05$ for low dose $KBrO_3$ treated group vs. control group; $^{\#}P<0.05$ for high dose $KBrO_3$treated group vs. control group; $^{+}P<0.05$ for high dose $KBrO_3$ treated group vs. low dose $KBrO_3$ treated group.

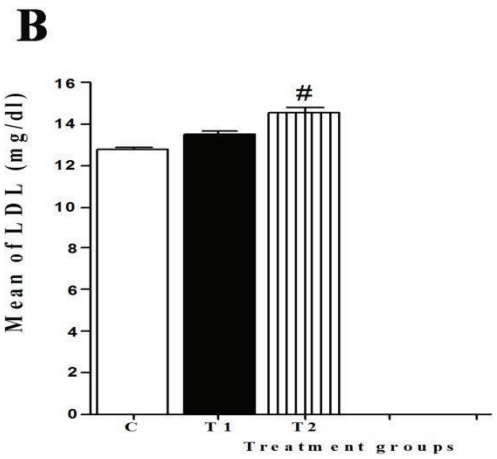
Table1:**Effect of $KBrO_3$ treatment on the RBCs, WBCs and platelets count** RBCs, WBCs and platelets count were measured in the three groups of mice, and the results are presented as the means ± SEM (n=10), $^{*}P<0.05$ for low dose $KBrO_3$ group vs. control; $^{\#}P<0.05$ for high dose $KBrO_3$ group vs. control.

Table1

	Mean Total Leukocyte Count ($x10^9$/L)	Mean Total Reticulocyte Count ($x10^9$/L)	Mean Platelet Count ($x10^9$ /L)
Control	11.3 ± 0.62	8.3352± 0.13200	875±38
$KBrO_3$ (100mg/dl)	10.0 ± 0.58*	7.2550± 0.3294*	423 ±42*
$KBrO_3$ (200mg/dl)	9.5 ± 0.93#	7.1375±0.4019#	405±63#

Figure 1





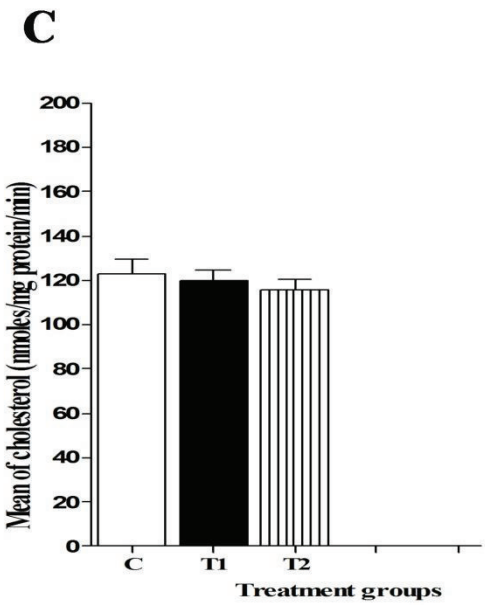


Figure2

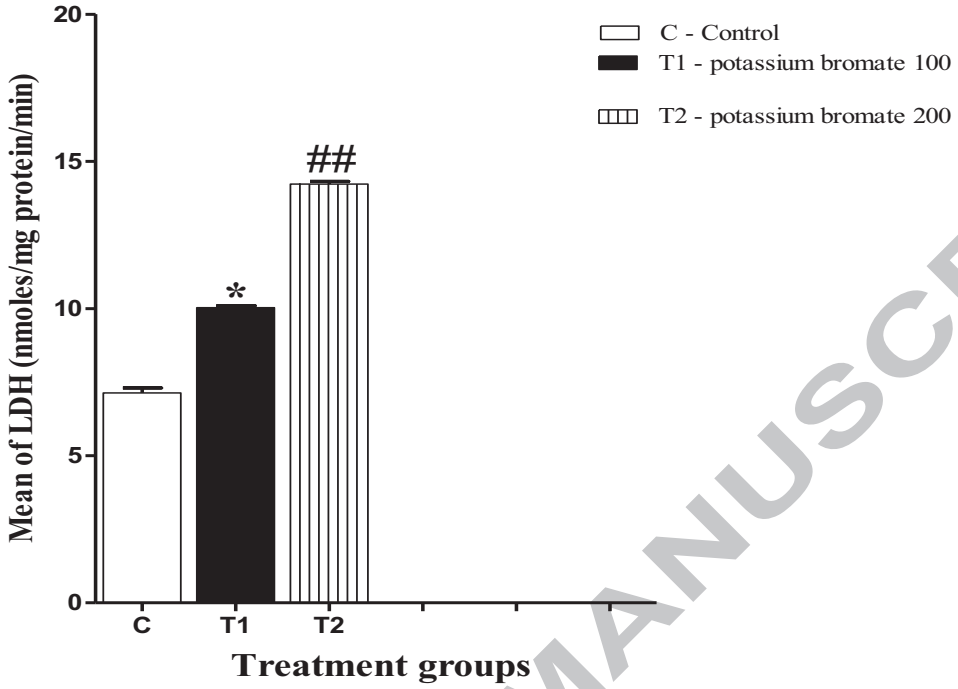


Figure3

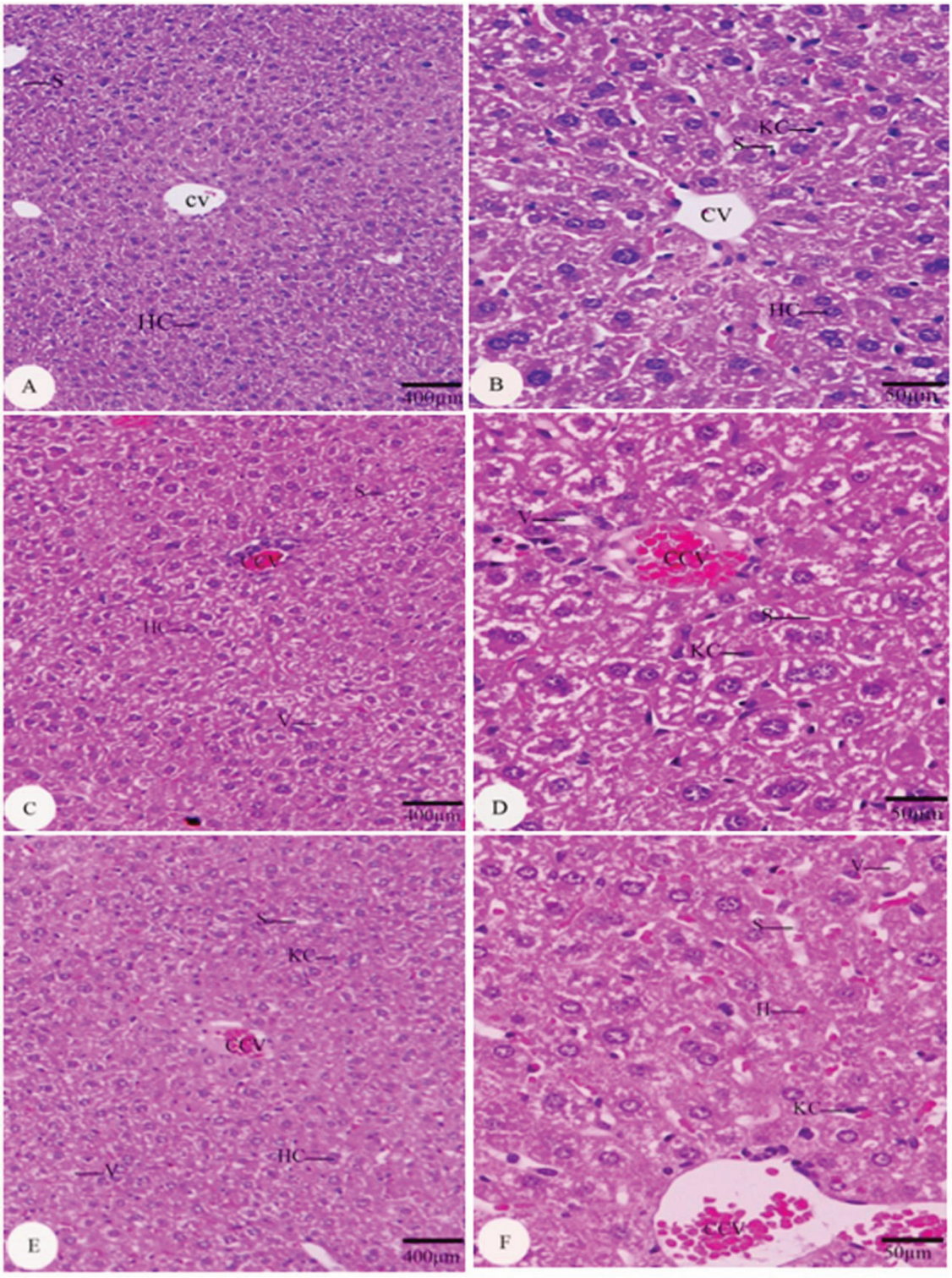


Figure4

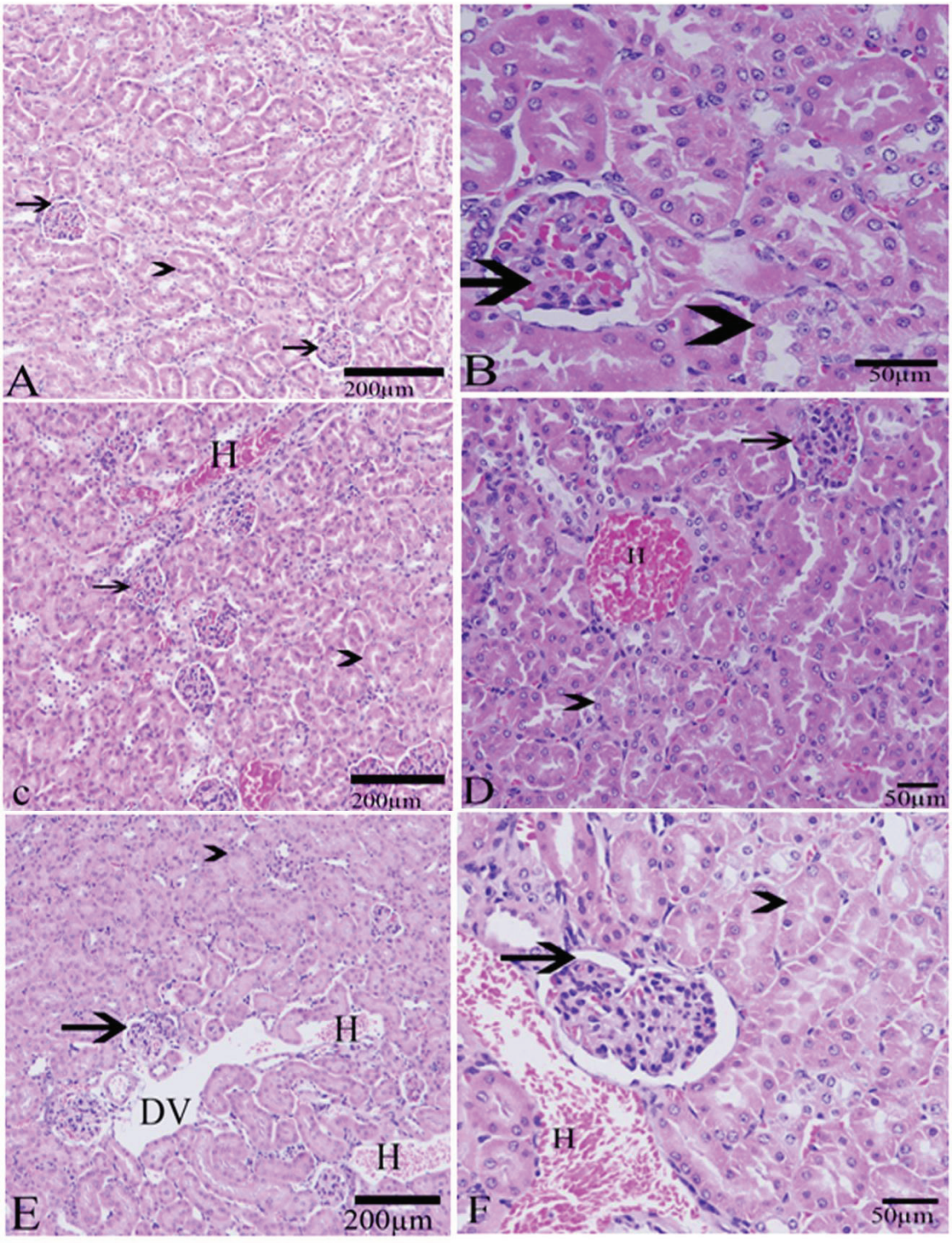


Figure5

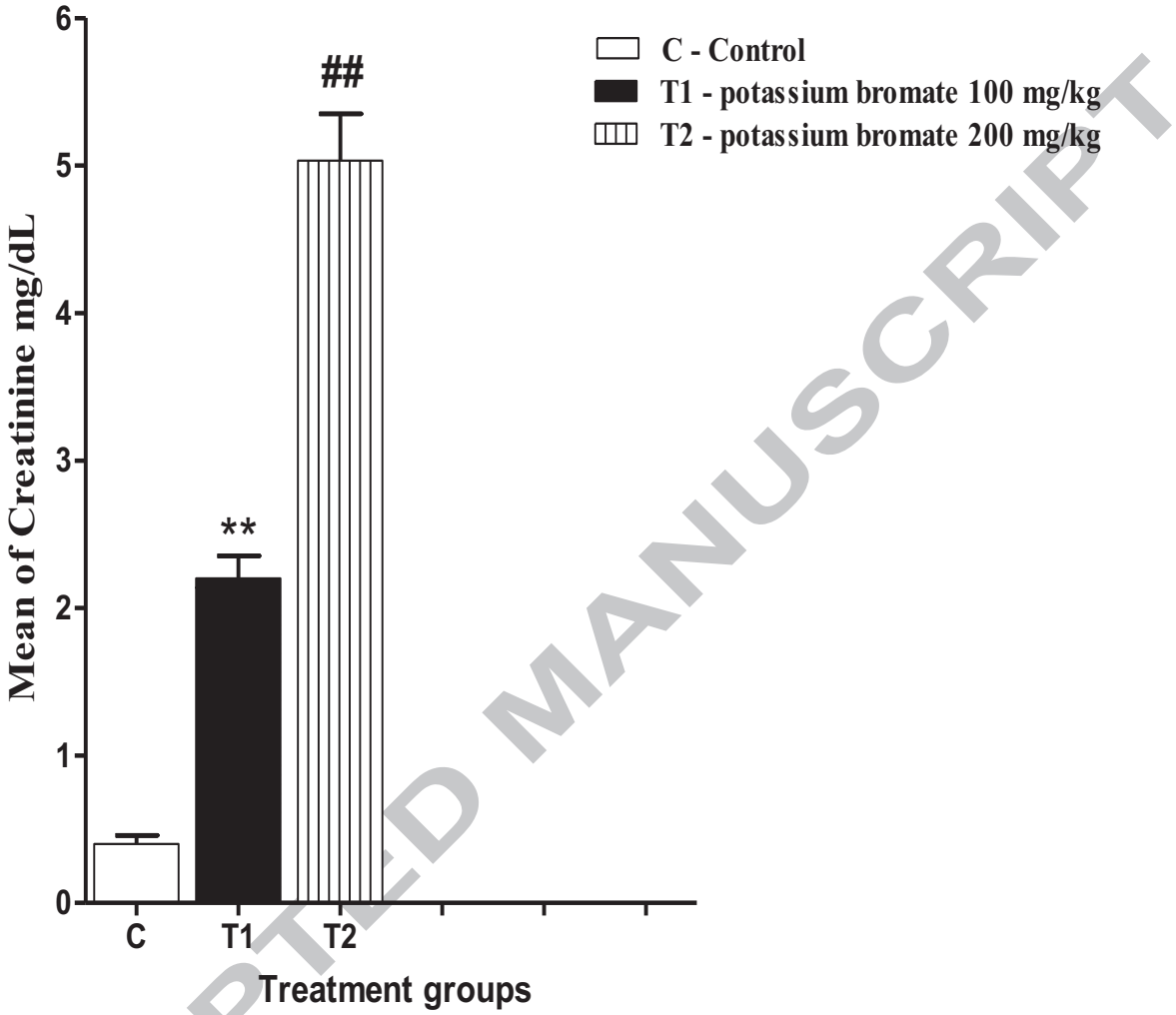


Figure6