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Protective Effect of *Allium cepa* L.(onion) Against Potassium Bromate-Induced Hematological, Biochemical and Histopathological Alterations in Rats

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Abstract:- Onion (*Allium cepa* L.) is one of the most widely consumed and cultivated vegetable crops in the world, which are effective antioxidants due to their capability to scavenge free radicals. Potassium bromate is a chemical additive mixed in flour to improve the action of gluten and helps to strengthen and soften the dough. Several studies have shown that a higher amount of Potassium bromate can cause toxicological effects and several diseases. The study aims to investigate the protective and curative effects of red onion extract against $KBrO_3$ toxicity on hematological, renal function and histology of the kidney tissues of Wistar rats. 36 Wistar male rats were divided into 6 batches. Over a 4-week experimental period, group I rats served as a control and group II received 100 mg/kg b.w of $KBrO_3$ on the 24th and 27th days. group III received red onion juice at 1ml/100 g bw every day and 100 mg/kg bw of $KBrO_3$ on the 24th and 27th days. Group IV received 50 mg/kg bw of $KBrO_3$ twice per week, group V received red onion juice daily at 1ml/100 g bw and 50 mg/kg bw of $KBrO_3$ twice per week, and group VI received 30 mg/kg $KBrO_3$ every day. The rats were weighed and sacrificed after completion of the treatment, and blood was sampled for haematological and biochemical analysis. The histopathological investigation was performed for the kidney tissues of all groups. The results showed a significant ($p<0.05$) increase in WBC in groups which received 30 and 50 mg/kg bw of $KBrO_3$ and a significant decrease in PLT in the group that received 100 mg/kg bw of $KBrO_3$ compared to the controls. Additionally, significant increases in urea, uric acid, creatinine, were found in all groups treated with $KBrO_3$. However, the administration of red onion juice along with $KBrO_3$ led to improvements in the parameters studied. Histopathological examination of kidney tissue showed dilation of the Bowman's capsule, haemorrhage, degeneration, congestion, and necrosis. it is clear that the toxic effects of $KBrO_3$ were more pronounced in rats receiving single doses of 100 mg/kg bw. This indicates that a higher dose leads to worse effects. The results for a regular dose of 30 mg/kg also indicate the risk of daily exposure to potassium bromate.

Keywords:- *Potassium bromate, histopathology, hematology, red onion, kidney, Wistar rats.*

I. INTRODUCTION

Potassium bromate ($KBrO_3$) is a chemical additive mixed in flour to improve the action of gluten. Gluten is a protein found in wheat flour that gives the dough of the bread elasticity during kneading and thereby encourages the fermentation of the dough by retaining the gases produced by yeast [1]. When it is used within prescribed limits of 15-30 ppm, it changes during the baking process and leaves no trace in the end product [2]. Ideally, therefore, the end product should contain no potassium bromate, which has been broken down during the baking process into potassium bromide (KBr), a harmless byproduct [3]. However, if the mixture includes higher amounts of potassium bromate, or if the bread is not fully cooked or has been baked at insufficiently high temperature, then residual amounts of $KBrO_3$ remaining in the bread would be harmful to health when consumed [4,5]. Indeed, several reports indicate toxicological effects and several diseases, including cancer [6,7]. $KBrO_3$ has been shown to be nephrotoxic in both human and experimental animals [8]. Although the kidney is considered to be the main organ affected by $KBrO_3$, it also causes severe tissue damage to many other organs of treated rats and mice including the liver, thyroid, testes and intestine [7,9,10]. Also, it induces kidney cancer, peritoneal mesotheliomas, and follicular cell tumours of the thyroid [6,11,12,13].

Several antioxidants (AOs) have shown protection against bromate-induced toxicity. These antioxidants could reduce or prevent free radical formation and disrupt the oxidation chain reaction and neutralize free radicals, leading to delays to or the inhibition of cellular damage [7,14,15,16].

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Onion (*Allium cepa* L.) is one of the most widely consumed and cultivated vegetable crops in the world [17], which are effective antioxidants due to their capability to scavenge free radicals [18]. Scientific reports have confirmed their functional properties, which include: antioxidant activity [19]; a hepatoprotective effect [20]; anti-carcinogenic, anti-infection properties [21] and other biological actions [22]. Therefore, the aim of this study was to investigate the effect of $KBrO_3$ on hematological, biochemical parameters and kidney of Wistar rats, and to observe any protection provided by red onion extract against $KBrO_3$ toxicity.

II. MATERIALS AND METHODS

➢ *Animals*

Albino Wistar rats (12–13 weeks old, weighing 150–200g each) were obtained from the Animal House of the National Medical Research Centre in the city of Al-Zawia, Libya. 30 male Wistar rats were randomly allocated to 5 groups of 6, where each group was subjected to one of the treatments as prescribed later. They were housed in standard clear plastic cages and maintained under standard animal housing conditions. They were allowed to acclimatize for 2 weeks before the experiments were conducted, and were given free access to standard laboratory food and water. All animals were grown for the four-week period of the experiment.

➢ *Preparation of Red Onion Extract and Potassium Bromate*

Fresh onion, *Allium cepa*, was obtained from the local market in Al-Zawia. The bulbs were rinsed thoroughly with water and cut into small pieces. Extract (AcE) was prepared daily following the procedures used in previous studies [23, 24]. Potassium bromate was purchased in powder form from the Sigma-Aldrich Company. Stock of potassium bromate (KBrO3) solution was prepared to the required concentrations as needed.

➢ *Experimental Animals Grouping*

The animals were divided into 5 equal groups, each contains 6 male rats:

1) ***Control Group (*G1):** Rats were fed with a normal diet and drinking water only for four weeks.
2) **Treated *Group 2* (G2):** Rats were given $KBrO_3$ by oral gavage (100 mg/kg bw) at days 24 and 27 of the experiment.
3) (AcE + $KBrO_3$) ***Group3* (G3)**: Rats were treated with 1 mL/100 g bw/day of AcE extract via gavage for 28 days + $KBrO_3$ (100 mg/kg b w) at days 24 and 27 of the experiment.
4) ($KBrO_3$) ***Group 4* (G4)** rats were given $KBrO_3$ by oral gavage in doses of 50 mg/kg bw twice per week**.**
5) ($KBrO_3$ + AcE) ***Group 5* (G5)** rats were treated with (1 mL/100 g bw/day) of AcE extract via gavage for 28 days+ $KBrO_3$ (50 mg/kg bw) twice a week.
6) ($KBrO_3$) ***Group6* (G6)** rats were given $KBrO_3$ by oral gavage in doses of 30 mg/kg bw/day) for 4 weeks.

➢ *Sample Collection and Biochemical Analysis*

At the end of the 28-day experimental period, the rats were fasted overnight and sacrificed 48h after the last treatment. Rats were sacrificed under chloroform anaesthesia and quickly dissected. Blood samples were collected directly from the animals by heart puncturing prior to the excision of the required organs. Blood was withdrawn from the heart into 2 tubes: heparinized tubes for the complete blood count (CBC), and plain tubes for biochemical tests. The levels of urea, uric acid and creatinine, were determined.

➢ *Preparation of Tissue Samples*

Portions of the kidney were immediately fixed in 10% neutral buffered formalin for histological study. Tissues were dehydrated through a series of ethanol solutions, cleared in xylene, embedded in paraffin and routinely processed for histological analysis [25]. Sections of 5 µm thickness were cut using a rotary microtome and stained with haematoxylin-eosin for general histological examination.

➢ *Statistics*

Data were subjected to one-way ANOVA using GraphPad Prism. The data are presented as mean ± SEM. The cut-off value for statistical significance was $p < 0.05$ and indicated with asterisks.

II. RESULTS

➢ *Hematological Parameters in Rats*

The mean±SE of hematological values from different samples of each group are presented in Table (1) and Figs (1 A&B). However, there were variations in RBC and HGB; the differences were not statistically significant with those of the normal values. On the other hand, statistically ($P < 0.05$) results showed that the WBC increased when $KBrO_3$ (50 or 30 mg/kg bw) was administered to rats as compared with normal control. However, when $KBrO_3$ was concurrently administered with juice of red onion, it resulted in decreases in WBC towards normal control values. The results show also a significant decrease in PLT in $KBrO_3$ treated group (100 mg/kg bw) compared with the control group (Table 1& Fig. 1). No significant difference was observed between PLT of all other groups and control.

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TABLE 1: Effects of $Kbro_3$ on Hematological Parameters, and the Role of the Protection Provided by Red Onion Juice Against $Kbro_3$ Toxicity in Male Albino Rats.

Parameters / Groups	WBC (mean±SE)	RBC (mean±SE)	HGB (mean±SE)	PLT (mean±SE)
Control	4.42± 1.23	7.56± 0.16	13.6±0.15	563.8±31.38
$KBrO_3$ (100 mg/kg bw)	6.46±061	8.11± 0.55	14.06±1.02	348.4±16.57*
AcE + $KBrO_3$ (100 mg/kg bw)	8.74±1.38	8.05± 0.42	13.44±0.75	414±50.77
$KBrO_3$ (50 mg/kg bw)	14.12±2.51***	8.52± 0.38	14.94±0.60	689.2±106
AcE + $KBrO_3$(50 mg/kg bw)	4.26±0.48	8.20± 0.18	14.06±0.27	606±5.74
$KBrO_3$ (30 mg/kg bw)	10.48±1.71*	8.16± 0.14	14.14±0.15	689±17.17

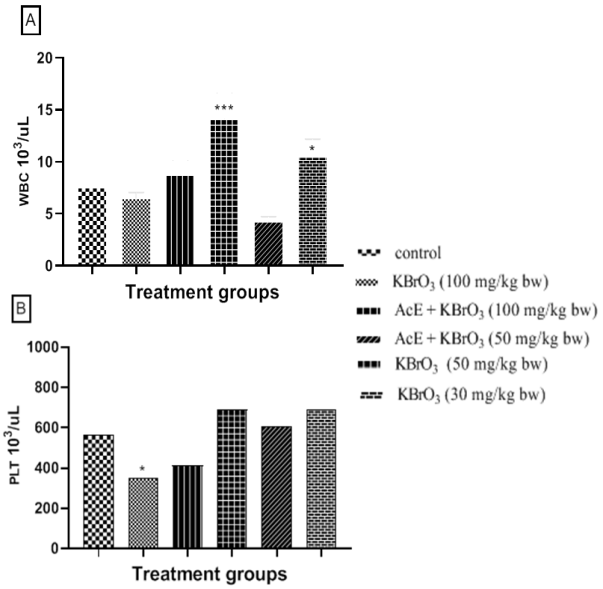

Fig. 1. Effects of $KBrO_3$ on hematological parameters and the role of pretreatment with red onion juice against toxicity KBrO3 in male albino rats compared with the control group.

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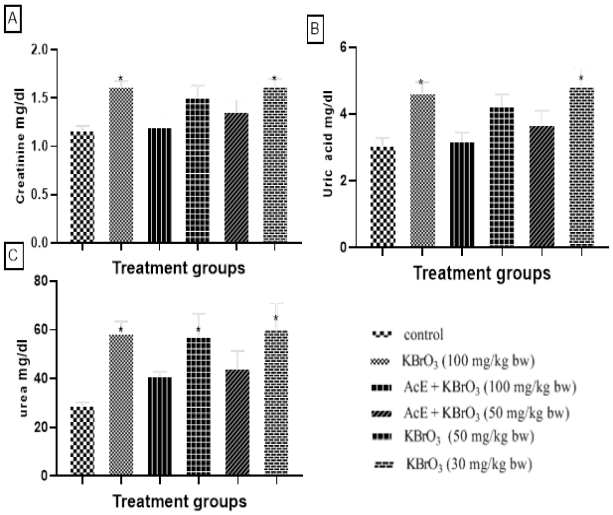

Fig. 2. effects of $KBrO_3$ on kidney function in terms of serum urea, creatinine and uric acid concentrations, and the protection provided by red onion juice against $KBrO_3$ toxicity in male albino rats compared with the control group
.* $P < 0.05$ Statistically significant difference compared to the control group.

➢ *Biomarkers of Renal Function*

For the assessment of kidney functioning, serum urea, creatinine and uric acid content were estimated. In $KBrO_3$-treated rats, renal functional markers such as creatinine, urea and uric acid were increased remarkably in the $KBrO_3$ group compared to the control rats ($P < 0.05$) indicating the clear dysfunction caused by $KBrO_3$ exposure. These biochemical parameters were improved after treatment with the red onion juice. The level of the markers was lower in (AcE + $KBrO_3$) treated rats compared with the $KBrO_3$ group (Figs. 2. A, B and C).

➢ *Concentrations of Sodium and Potassium Ions*

Sodium and Potassium Ions were also measured in this study. The results show a significant increase in sodium and potassium concentrations only when rats were treated with 30 mg/kg bw of $KBrO_3$ daily throughout the experimental period compared with the control group, as shown in Fig. 3. The mean values of the electrolytes (Na^+ = 158.8±8.8; K^+ = 7.22±0.52) increased when rats were treated with 100 mg/kg bw of $KBrO_3$; however, the difference was not significantly different compared to the control value (Na^+=138±2.59; K^+=5.52±0.11). Pretreatment with red onion juice seemed to shift these parameters toward normal values.

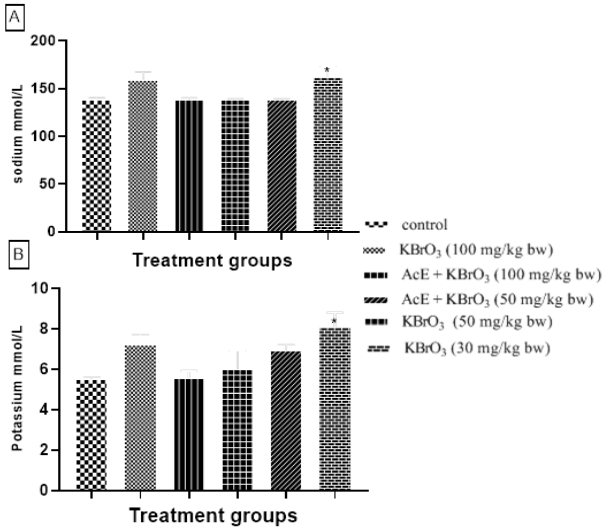

Fig. 3. Effect of $KBrO_3$ on kidney serum concentrations of sodium and potassium ions, and the protection provided by red onion juice against toxicity $KBrO_3$ in male albino rats compared with the control.
* $P < 0.05$ Statistically significant difference compared to the control.

➢ *Effects of Treatment on Histology of Kidney Tissues*

Renal tissue from all the experimental and control rats were examined using a light microscope. In the non-treated group, the microscopic observation of kidney sections displayed the normal architecture of both the renal corpuscles and tubules, as shown in Figure 4A. In addition, the renal histological examination showed no tissue degeneration, inflammation, necrosis, or tubular dilation. However, the histology of the kidneys of rats treated with 100 mg/kg of $KBrO_3$ shows degenerative changes in the renal tubules indicated by tubular destruction and the detachment of tubular epithelial cells. In addition, glomerular changes included the dilation of the Bowman's space and haemorrhaging (Fig. 4b). The administration of 50 mg/kg of $KBrO_3$ twice per week caused irregular glomerular morphology, hemorrhages, degeneration and necrosis. The desquamation of epithelial tubular cells was also observed, with a loss of the brush border as indicated with arrowheads in Fig. 4d. Significant changes in the group treated with 30 mg/kg/day of $KBrO_3$ apparent in Fig. 4F, showing dilation in Bowman capsules and tubules (black arrows), shrinkage of the glomerular tuft (red arrow), capillary congestion (blue arrow) and severe necrosis of the tubular cells (yellow arrow. In contrast, the $KBrO_3$ + red onion juice group showed apparently mild to moderate tubular epithelial changes and less damage in histological architecture of renal corpuscles and glomerular tuft surrounded by Bowman's space (Figs 4C & 4E). There was also little tubular damage compared to group treated with $KBrO_3$ alone.

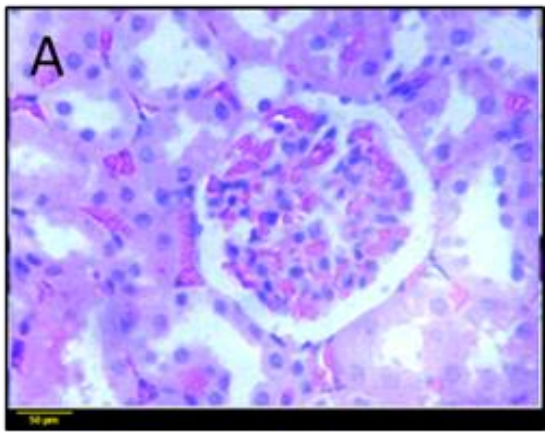

Fig. 4(A). Light micrographs of hematoxylin & eosin staining of kidney tissues of control group shows normal histology (x400).

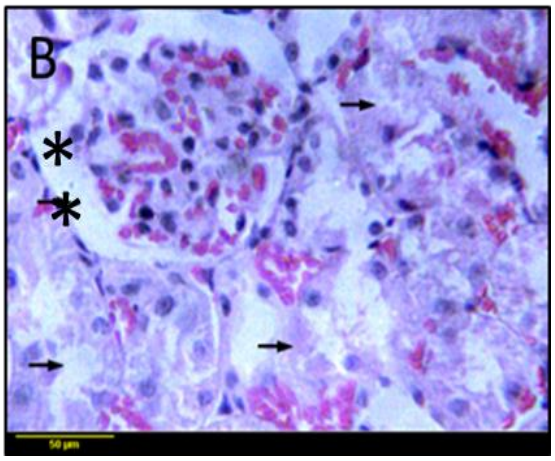

Fig. 4(B) Rats treated with $KBrO_3$ (100 mg/kg bw) show degenerated glomeruli (black arrows) and dilation of Bowman's space (Asterisk) (x400).

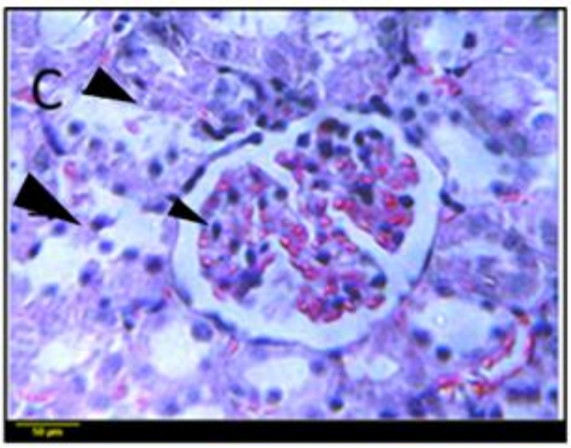

Fig. 4(C). Section of treated group by AcE + $KBrO_3$ (100 mg/kg bw) shows less damage (arrowheads) in glomerulus and tubules (x400).

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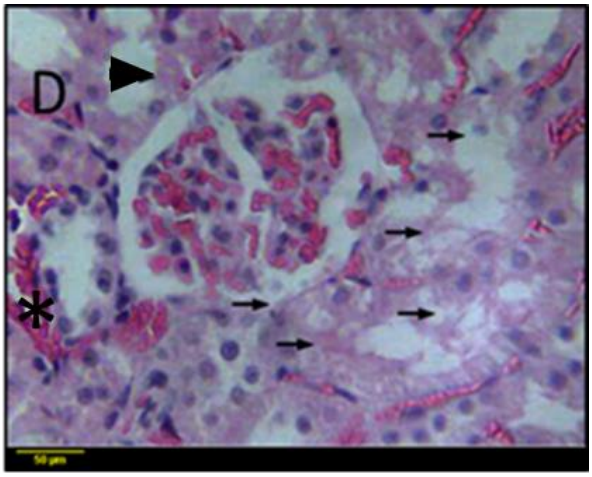

Fig. 4(D). Irregular glomerular morphology, hemorrhage (Asterisk) and degenerated tubular (arrows) with loss of brush border (arrowheads) are seen in rats receiving $KBrO_3$ (50mg/kg bw) (x400).

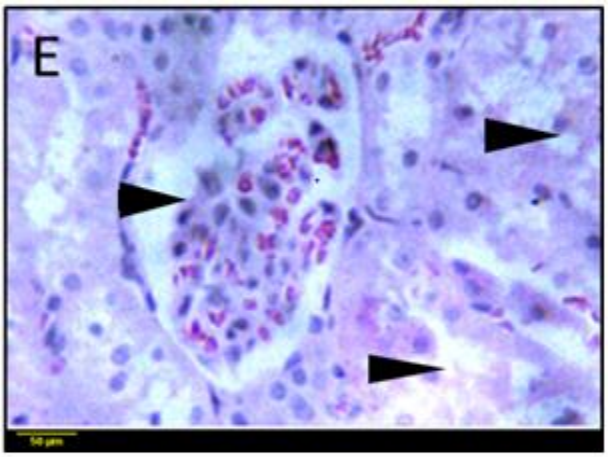

Fig.4 (E). AcE + $KBrO_3$ (50mg/kg bw) treated group (x400) shows moderate damage (arrowhead).

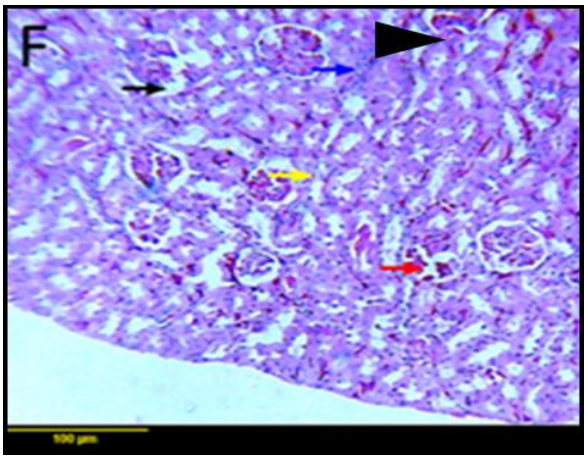

Fig. 4(F) Dilatation in Bowman capsule (black arrows), shrinkage of glomerular tuft (red arrow), capillary congestion (arrowhead), infiltration (blue arrow) and severe necrosis of tubular cells (yellow arrow) are seen in rats receiving $KBrO_3$ (30 mg/kg bw) (x100).

III. DISCUSSION

The results of the present study showed a significant increase in WBC, which might associated with inflammatory conditions due to the effect of $KBrO_3$ and similar chemicals [26]. It is also observed that $KBrO_3$ does not affect the red blood cell (RBC) count or haemoglobin level (Hb%), which contrasts with [27] who observed significant decreases in these parameters after rats were treated with a 100 mg/kg bw dose of $KBrO_3$ Rats in $KBrO_3$-administered groups showed a notable decline in platelets (PLT) as compared to the controls. PLT play an important role in blood clotting and prevent blood loss from haemorrhaging. Potassium bromate may thus adversely affect platelet levels. Similar results were reported [28,29]. These reductions in PLT could be due to the DNA strand breaking in cells, induced by the oxidative stress associated with $KBrO_3$ [30]. However, the pre-treatment of animals with red onion juice improved the haematological parameters. PLT content improved, while a significant reduction in the WBC count down to a normal level was noted. These findings are in agreement with earlier studies, including [29,31]. This effect may indicate an activation of the animal's immune system in reaction to tissue damage caused by any toxicant [32].

In the current study, treatment with $KBrO_3$ also induced significant increases in some renal function biomarkers compared with other groups, including urea, creatinine, uric acid, and sodium and potassium ions. This is an indication of severe kidney damage, which was also observed in terms of pathological differences in kidney parameters. Similar results were reported [14]. Increases in serum creatinine and urea are damage indicators concerning poor glomerular filtration and have been recognized as major biomarkers of kidney dysfunction and the loss of integrity of the renal tubules [33]. Also, [34] stated that rising levels of urea have been linked with renal failure. The increase in uric acid levels may also be due to the degradation of purines and pyrimidines which are strongly linked to a surge in xanthine oxidase activity, causing the overproduction of uric acid and also the production of reactive oxygen species (ROSs) [27].

However, the administration of red onion juice reversed the abnormal amounts of creatinine, urea, and Na^+ and K^+ electrolytes in rats in the $KBrO_3$ + AcE group whose levels were not significantly different from the controls. This suggests a possible protective effect of red onion against $KBrO_3$-induced renal damage. This finding is in line with [35], where the total antioxidant status of hyperuricemic rats increased after receiving 5 g/kg/day of onion for 2 weeks, as well as [36] where a larger dose of 10.5 g/kg/day of onion juice decreased the serum uric acid level in hyperuricemic rats. The hypouricemic effects of onion juice might be due to the presence of flavonoids which exert inhibitory effects on XO and xanthine dehydrogenase enzyme activities [36]. Moreover, the rich flavonol content of red onion, with 32 phenolic compounds, is believed to be responsible for antioxidant activity such as the reduction of uric acid in the blood [37]. However, despite the potential benefits of red onion, some experiments have identified possible negative effects in mice after the consumption of aqueous red onion

extract over 56 days [38]. In order to investigate the nephrotoxic effect of oral doses of $KBrO_3$ in rats and the possible ameliorative effect of pre-treatment with red onion extract, histological staining was performed.

The histopathological results observed in the present study support the biochemical results and indicate that $KBrO_3$ induces severe histological alterations in kidney tissue. Similar changes have been recorded by other investigators [27,39]. The histopathological results in this study revealed that oxidative damage to kidney tissues was evident in rat groups treated with different doses of potassium bromate. This included the dilatation of the Bowman capsule, glomerular shrinkage, and haemorrhage associated with tubular degeneration, as well as marked necrotic changes and loss of the brush border. In contrast, pretreatment with red onion led to significant amelioration of the significant pathological changes induced by $KBrO_3$ administration. This could be attributed to the antioxidant and anti-inflammatory characteristics of red onion, which significantly reduces oxidative stress leading to a restoration of the normal physiological state of kidney cells [27]. Moreover, bioactive compounds in red onion may provide further improvements to these pathological changes in the renal tissue of $KBrO_3$-treated rats [39]. Similar observations have been reported in an earlier study [5], which confirmed that treatment with 100 mg/kg/day of vanillin for 15 days restored the histopathological changes in $KBrO_3$-induced kidney damage.

The histopathological changes seen in the renal tissues of $KBrO_3$-induced nephrotoxic untreated group further confirm the renal injury which might be activated by oxidative damage. Previous studies have indicated that $KBrO_3$ may initiate glomerular injury, tubular necrosis, and other damage [27,34,40]. This is in line with the findings of the current study which indicate the degeneration of corpuscular tissues after $KBrO_3$ administration in the $KBrO_3$-induced nephrotoxic untreated group in comparison with the control.

IV. CONCLUSION

The current study investigated the protective role of red onion juice against KBrO3-induced oxidative stress in heamatological parameters, renal function biomarkers and histopathology of kidney. In this study, bromate-incited nephrotoxicity in rats led to changes in renal tissues, as demonstrated by changes in some kidney biomarkers and biochemical parameters. $KBrO_3$ caused increases in the levels of urea, uric acid, creatinine and sodium in the serum, which reflect reductions in glomerular filtration and tubular damage. $KBrO_3$ also induced haematological changes such as a significant increase in WBC and a decrease in PLT, which occur due to the harmful effects of $KBrO_3$ on the bone marrow and haematopoietic organs. The histopathology results for KBrO3-treated rats showed pathological alterations in the renal capsule, the Bowman's space. Thus, red onion has been found to contain substances providing higher antioxidant activity compared to other vegetables. Thus, it is believed that the consumption of red onion increases the total antioxidant status of rats.

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DISCLOSURE STATEMENT

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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