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Original article

Nephrotoxicity of Potassium Bromate and Ameliorating Role of *Ruta chalepensis* on kidney Weight and Some Biochemical Parameters of Male Rats

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ABSTRACT

Background and aims. *Potassium bromate ($KBrO_3$), used as food additive in the manufacturing of bread, is proven hazardous for the human health. Ruta chalepensis (R. chalepensis) is used in Mediterranean folk medicine to treat pulmonary conditions, for example tuberculosis, and to decrease swelling of the spleen, as well as outwardly to treat wounds. The present study aimed to investigate the protective and curative effect of R. chalepensis against $KBrO_3$ toxicity on kidney weight and some biochemical parameters of male rats.* ***Methods****. Fifty male albino rats were divided into five groups. The first group served as control animals. The second group was administered R. chalepensis at an oral daily dose of 0.5 g/Animal for four weeks. The third group received $KBrO_3$ at an oral daily dose of 100 mg/kg/b. w. for four weeks. The fourth group (protective group) administered with R. chalepensis alone for 2 weeks and followed by R. chalepensis in association with $KBrO_3$ for 2 weeks. The fifth group (therapeutic group) was first given $KBrO_3$ alone for 2 weeks and was secondly administered $KBrO_3$ in association with R. chalepensis for 2 weeks. After 2^{nd} and 4^{th} weeks of treatment, the determination of kidney weights and relative kidney weight were calculated. Also, the sera were collected for biochemical assays.* ***Results****. The results of the present study showed significant increase in the mean kidney weight in $KBrO_3$ group at 2 weeks and therapeutic groups at 2 and 4 weeks compared to the control group. In addition, significant increase in relative kidney weight in $KBrO_3$ group after 2 and 4 weeks, and therapeutic group after 2 weeks. While, there was decrease in relative kidney weight in R. chalepensis group after 4 weeks. Furthermore, serum urea levels significantly increased after 2 weeks in $KBrO_3$ and therapeutic groups. A significant increase in serum urea levels showed in all groups except R. chalepensis group, which revealed a slight decrease after 4 weeks. No changes in serum creatinine levels in all groups after 2 weeks. In contrast, protective and therapeutic groups revealed significant elevation in serum creatinine levels after 4 weeks.* ***Conclusion****. It may be concluded the toxic effects of $KBrO_3$ on kidneys and minimal ameliorative effects of R. chalepensis.*

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INTRODUCTION

Potassium bromate ($KBrO_3$) is widely used as a food additive in the bread making processes and found in drinking water samples as a byproduct of ozone disinfection. $KBrO_3$ also used in fish paste, cheese, and beer production. Moreover, it is used in pharmaceutical and cosmetic industries and it is a constituent of cold-wave hair solutions [1]. Since the kidney is the primary target organ of $KBrO_3$, the toxic effects of $KBrO_3$ in humans arise from acute poisoning causing renal failure [2]. $KBrO_3$ causes nephrotoxicity and renal cell cancer in rats. It was found to be a genotoxic and carcinogenic [1,3]. The $KBrO_3$ induces renal oxidative stress and cause renal failure and kidney cancer [4]. According to The National Institute of Health, the toxicity and carcinogenicity of $KBrO_3$ is stated as follows: It proves to be a carcinogenic agent and nephrotoxic in both rats and humans. $KBrO_3$ also proves to induce renal cell tumors. Many scientific experiments and researchers aimed at elucidating the mode of carcinogenic action reveals that $KBrO_3$ is a potent carcinogen, possessing both initiating and promoting symptoms for rat renal tumorigenesis [5]. $KBrO_3$ causes nephrotoxicity and hepatotoxicity in rats [6,7].

Administered single intra-gastric dose of $KBrO_3$ to rats at 300 mg/kg b. w. showed significant increase in relative kidney weight, while the body weight and relative liver weight did not change affected [8]. *Ruta chalepensis* (*R. chalepensis*) is a species of citrus family commonly named as fringed rue. It is native to Eurasia and North Africa. *R. chalepensis* is extensively used throughout the world as an herbal remedy for various illnesses [9]. *R. chalepensis* is a perennial herb, widely distributed in the Mediterranean area, growing in dry, usually rocky areas. It is an ancient medicinal plant still used in the traditional medicine of many countries as a laxative, anti-inflammatory, analgesic, antispasmodic, abortifacient, antiepileptic, emmenagogue and for dermatopathy treatment [10]. Additionally, Rue used as a uterine stimulant to encourage onset of menstruation. The leaf of rue is said to alleviate cancer of the mouth, as well as tumors and warts. In Chinese medicine, rue is used as a vermifuge and for insect bites [11]. Gheth *et al.* [7] reported the ameliorative effect of *R. chalepensis* when administrated for protective and therapeutic purposes against $KBrO_3$ hepatotoxicity. In a recent study of *R. chalepensis* oil extract against $KBrO_3$ toxicity on testes of rats. Gheth *et al.* [12] showed no changes in the mean body weight, testis weight and relative testis weight among control and all treated groups of rats after 2 and 4 weeks. The present study aimed to investigate the protective and curative effect of R. chalepensis against KBrO3 toxicity on kidney weight and some biochemical parameters of male rats.

METHODS

Animals

Fifty male albino rats (*Rattus norvegicus*), weighing between 275-300 g were used throughout the present study. They were obtained from the animal house of Department of Zoology, Faculty of Science, Omar Al-Mukhtar University, Libya. The animals were housed in five groups in standardized cages and were located in the same room with constant environmental conditions such as temperature (22 ± 3°C) and humidity (50 - 60 %). They were supplied with enough rat feed and drinking water *ad-libitum*. All animals were allowed to acclimatize in the environment for two weeks before the commencement of the study.

Preparation of potassium bromate

Potassium bromates with the empirical formula $KBrO_3$ obtained from (BDH) company (England). $KBrO_3$ was orally administrated at a dose 100 mg/kg/b.w., and dissolved in distilled water freshly prepared [13] daily for 2 and 4 weeks according to the group distribution.

Preparation of Ruta chalepensis

Leaves of *R. chalepensis* were collected from Al-Jabal Al-Akhdar region on the east coast of Libya. The extraction process for the *R. chalepensis* essential oil followed the methodology described by [14].

The collected leaves were weighed, washed with water, dried and then placed in acetone inside sealed jars for 48 hrs. Solvent was removed from samples by rotary evaporator and then oils were collected. *R. chalepensis*was orally administrated at dose of 0.5 g/Animal [15], daily for 2 and 4 weeks, which represents the overall experimental duration. Both doses were orally given through a special stomach tube with a smooth tip to protect the interior lining of the oral and buccal cavity from injury.

Experimental animals grouping

The animals were divided into 5 equal groups, each contains 10 male rats: 1) Control group: Animals of this group received distilled water daily by oral gavage for four weeks. 2) *R. chalepensis* treated group: Rats received *R. chalepensis* oil extract orally in a daily dose of 0.5 g/Animal, for four weeks. 3) $KBrO_3$ treated group: This group-included rats that were administrated $KBrO_3$ in a daily dose of 100 mg/kg b. w. for four weeks. 4) Protective group: Animals of this group were first administrated *R. chalepensis* oil extract daily for two weeks and secondly administrated daily oral doses of *R. chalepensis* oil extract in association with $KBrO_3$ for an additional two weeks. 5) Therapeutic group**:** Animals of this group were first provided with oral dose of $KBrO_3$ daily for two weeks, and then were treated orally with $KBrO_3$ in association with *R. chalepensis* oil extract for an additional two weeks.

Determination of Absolute and relative kidney weigh

Rats from control and treated groups were weighed and slaughtered. The kidney weight was calculated relative to the total body weight, consequently:

$$Relative\ kidney\ weight = \frac{Absolute\ \ kidney\ \ weight}{Total\ \ body\ \ weight} \times 100$$

Preparation of serum samples

At the end of 2nd and 4th weeks, the animals were slaughtered. Their blood samples were collected individually in glass tubes. Serum was separated by centrifugation for 10 minutes at 3000 rpm. The resultant sera were collected for biochemical analysis.

Determination of serum urea level

Blood urea was determined according to the method of Fawcett and Scott [16] by using commercial kit purchased from Randox, U. K.

Determination of serum creatinine levels

Serum creatinine was determined using kit supplied by Stanbio, U. S. A. and according to the method of [17].

Statistical Analysis:

Analysis of variance one-way (ANOVA) was conducted to determine the difference among means. Means were separated using Tukey's test at P<0.05. The T test also used for compared between two means. All of the above data using Minitab statistical package program (Minitab version 17).

It is obtained from the following equation:

$$Percent\ of\ change = \frac{Mean\ \ of\ \ unknown\ -\ \ Mean\ \ of\ \ control}{Mean\ \ of\ \ control} \times 100$$

RESULTS

Kidney weight

The data in Table (1) and figure (1) showed no changes in the mean kidney weights between control, *R. chalepensis* and protective groups at 2 weeks. On the other hand, the mean kidney weight of $KBrO_3$ and therapeutic groups significantly increased and reached 1.11±0.13 g (27.59 % increase) and 1.08±0.13 g (24.14 % increase), respectively after 2 weeks compared to the control group. Furthermore, no changes were shown in the mean kidney weight in all groups except therapeutic group after 4 weeks. The mean kidney weight recorded in *R. chalepensis* group reached 0.84±0.08 g (-9.68 % decrease), $KBrO_3$ group reached 1.05±0.07 g (12.90% increase) and protective group reached 1.02±0.06 g (9.68 % increase) at 4 weeks. Nevertheless, a significant increase occurred in the mean kidney weight in therapeutic rats' group as compared to control group. The percentage of the mean kidney weight reached 26.88 % after 4 weeks. No marked changes in the mean kidney weight recorded for all groups when compared between 2 and 4 weeks in the same groups.

Relative kidney weight

The average of kidney weight to body weight ratio for each group is shown in table (1) and figure (2). No significant differences were found in the relative weight of kidney between control rats and those treated with *R. chalepensis* and protective groups after 2 weeks. In $KBrO_3$ and therapeutic groups, showed a significant increase in the relative kidney weight which reached 0.40±0.00 g (29.03 % increase) and 0.42±0.00 g (35.48 % increase), respectively after 2 weeks. No differences were found in the relative weight of kidney between control rats and those in protective and therapeutic groups after 4 weeks. Data of treated rats in *R. chalepensis* group reported decrease in the relative kidney weights with 0.29±0.01 g (-12.12 % decrease) at 4 weeks. On the other hand, the relative kidney weight increased in $KBrO_3$ group to 0.38±0.02 g (15.15 % increase) at the end of experimentation (4 weeks). No marked changes in the mean relative kidney weight recorded for all groups when compared between 2 and 4 weeks in same groups, except therapeutic group which recorded highly significant decreased when compared between 2 and 4 weeks.

Serum urea levels

Data recorded for the serum urea levels are presented in table (1) and figure (3). Control rats showed more or less constant levels during the course of the study. Moreover, no remarkable changes were reported in *R. chalepensis* and protective treatments groups in serum urea levels when compared with control group after 2 weeks. On the other hand, in $KBrO_3$ and therapeutic groups, a very highly significant elevation was realized in serum urea levels as compared with control group. The percentage elevation was 182.67 % and 167.90 % respectively, after 2 weeks. In *R. chalepensis* group the serum urea levels recorded a slight decrease which reached 16.00±2.48 mg/dl at percentage (-15.57 %) as compared to control group after 4 weeks. In the $KBrO_3$ and protective groups the urea levels recorded a highly significant increase after 4 weeks when compared to control which reached 30.50±2.59 mg/dl (60.95 % increase) and 37.25±1.79 mg/dl (96.57 % increase) respectively. Whereas, a significant increase in the serum urea level was reported in therapeutic group with 25.60±2.10 mg/dl (35.09 % increase) when compared with control group at the end of the experiment (4 weeks). No marked changes in the serum urea levels were recorded for the control and *R. chalepensis* groups when compared between 2 and 4 weeks in the same groups, whereas, a highly significant decrease in $KBrO_3$ and therapeutic groups when compared between 2 and 4 weeks in the same groups. Moreover, the protective group showed a highly significant elevation when compared between 2 and 4 weeks in the same group (Table 1 and figure 3).

Serum creatinine levels

The levels of serum creatinine, is presented in table (1) and figure (4). Control rats designated more or less constant figures during the study period. No changes were verified in all groups for 2 weeks as compared with control at 2 weeks. In *R. chalepensis* and $KBrO_3$ groups, no marked changes in the serum creatinine levels recorded after 4 weeks. In contrast, protective and therapeutic groups revealed significant increase in the serum creatinine levels when compared with control at the end of the experimental duration (4 weeks), which revealed 0.94±0.07 mg/dl (36.23 % increase) and 0.92±0.03 mg/dl (33.33 % increase) respectively. No marked changes in the serum creatinine levels were recorded for control, *R. chalepensis* and $KBrO_3$ groups when compared between 2 and 4 weeks in the same groups, whereas a significant increase in protective and therapeutic groups when compared between 2 and 4 weeks in the same groups (Table 1 and figure 4).

Table 1. The protective and therapeutic role of R. chalepensis oil extract against $KBrO_3$ toxicity on kidney weight (g), relative kidney weight (%), serum urea (mg/dl) and serum creatinine (mg/dl) levels.

Parameter	Group Duration		Control group	*R. chalepensis* group	$KBrO_3$ group	Protective group	Therapeutic group
Kidney weight	2nd week	Mean±S. E. % of change	$0.87^{B}{}_{a}$±0.01	$0.99^{B}{}_{a}$±0.05 13.80	$1.11^{A}{}_{a}$±0.13 27.59	$0.96^{B}{}_{a}$±0.05 10.34	$1.08^{A}{}_{a}$±0.13 24. 14
	4th week	Mean±S. E. % of change	$0.93^{B}{}_{a}$±0.02	$0.84^{B}{}_{a}$±0.08 -9.68	$1.05^{B}{}_{a}$±0.07 12.90	$1.02^{B}{}_{a}$±0.06 9.68	$1.18^{A}{}_{a}$± 0.02 26.88
Relative kidney weight	2nd week	Mean±S. E. % of change	$0.31^{B}{}_{a}$±0.01	$0.32^{B}{}_{a}$±0.01 3.23	$0.40^{A}{}_{a}$±0.00 29.03	$0.33^{B}{}_{a}$±0.01 6.45	$0.42^{A}{}_{a}$±0.00 35.48
	4th week	Mean±S. E. % of change	$0.33^{B}{}_{a}$±0.01	$0.29^{C}{}_{a}$±0.01 -12.12	$0.38^{A}{}_{a}$±0.02 15.15	$0.35^{B}{}_{a}$±0.01 6.06	$0.33^{B}{}_{b}$±0.01 0.00
Urea	2nd week	Mean±S. E. % of change	$18.75^{B}{}_{a}$±1.49	$16.75^{B}{}_{a}$±2.17 -10.67	$53.00^{A}{}_{a}$±6.52 182.67	$17.03^{B}{}_{a}$±2.17 -9. 17	$50.23^{A}{}_{a}$±6.52 167.90
	4th week	Mean±S. E. % of change	$18.95^{C}{}_{a}$±1.58	$16.00^{C}{}_{a}$±2.48 -15.57	$30.50^{A}{}_{b}$±2.59 60.95	$37.25^{A}{}_{b}$±1.79 96.57	$25.60^{B}{}_{b}$±2.10 35.09
Creatinine	2nd week	Mean±S. E. % of change	$0.67^{A}{}_{a}$±0.04	$0.60^{A}{}_{a}$±0.00 -10.45	$0.72^{A}{}_{a}$±0.03 7.46	$0.61^{A}{}_{a}$±0.00 -8.95	$0.70^{A}{}_{a}$±0.03 4.48
	4th week	Mean±S. E. % of change	$0.69^{B}{}_{a}$±0.05	$0.70^{B}{}_{a}$±0.04 1.45	$0.75^{B}{}_{a}$±0.02 8.70	$0.94^{A}{}_{b}$±0.07 36.23	$0.92^{A}{}_{b}$±0.03 33.33

A, B the groups in the same row with different letters are statistically significant ($p < 0.05$). a, b the groups in the same column with different letters are statistically significant ($p < 0.05$).

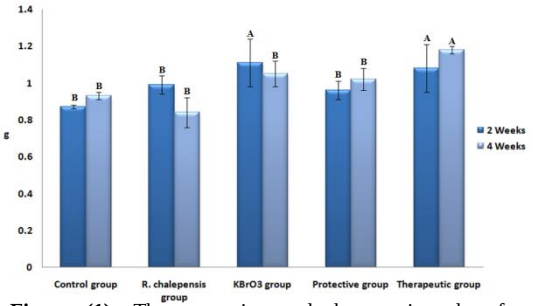

Figure (1): The protective and therapeutic role of *R. chalepensis* oil extract against $KBrO_3$ toxicity on kidney weight (g)

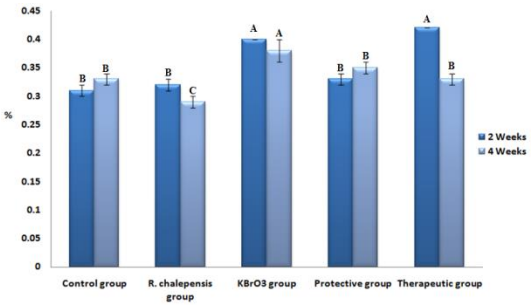

Figure (2): The protective and therapeutic role of *R. chalepensis* oil extract against $KBrO_3$ toxicity on relative kidney weight (%)

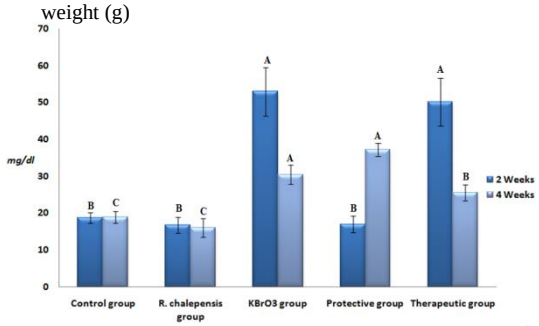

Figure (3): The protective and therapeutic role of *R. chalepensis* oil extract against $KBrO_3$ toxicity on serum urea (mg/dl) levels

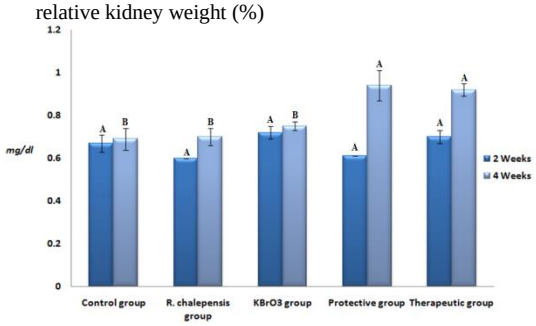

Figure (4): The protective and therapeutic role of *R. chalepensis* oil extract against $KBrO_3$ toxicity on serum creatinine (mg/dl) levels

DISCUSSION

$KBrO_3$ is a flour improver that acts as a maturing agent. It acts principally in the late dough stage giving strength to the dough. During the preparation of the dough, a network of protein molecules linked together by disulphide bonds is formed [18]. *R. chalepensis* is a rich source of several acridones and coumarins, as well as quinoline alkaloids [19].

The data in this study showed that no changes in the mean kidney weights between control, *R. chalepensis* and protective groups after 2 and 4 weeks and $KBrO_3$ group after 4 weeks. On the other hand, the mean kidney weight increased in $KBrO_3$ group at 2 weeks and therapeutic groups at 2 and 4 weeks compared to the control group. Which is in line with the previous work of Dodd *et al.* [20], they reported increases in kidney weights in rats. In the relative weight of kidney after 2 weeks no significant differences between control, *R. chalepensis* and protective groups. While, $KBrO_3$ and therapeutic groups showed a significant increase when compared with control. After 4 weeks, no differences between control, protective and therapeutic groups. In contrast, decrease in *R. chalepensis* group and increased in $KBrO_3$ group. The results of this study are in agreement with the results of Abuelgasim *et al.* [21]; they reported relative kidney weight increase in rats administered with 100 mg/kg b. w. of $KBrO_3$. In contrast, disagree with Abdelrahim *et al.* [22] on *R. chalepensis* was showed increase in the relative liver weight.

From published literature, we did not find any reports on effect *R. chalepensis* on experimental animals. Therefore, it could be that the duration of this study was short and the effect did not appear on the weight of animal kidneys. In the group treated with *R. chalepensis* no remarkable changes in urea and creatinine serum levels was detected after 2 and 4 weeks. Also, improvement was observed in protected rats' group in the same parameters. Results of the present study are in accordance with the findings of Adam *et al.* [23], they reported that oral administration of given seed *R. graveolens* ethanolic and aqueous extracts for 4 weeks did not cause any significant change in urea and creatinine levels. Administration of $KBrO_3$ resulted in impairment of some renal biomarkers reflected by the significant increase in urea after 2 and 4 weeks.

These results are in agreement with Oyewole [24] and Ahmed *et al.* [25], they reported that the $KBrO_3$ caused increased in urea levels. Urea is the major end product of protein catabolism and is primarily produced in the liver and secreted by the kidneys. It is the primary vehicle for removal of toxic ammonia from the body. Urea determination is very useful for the medical clinician to assess kidney function of patients [26]. In general, increased urea levels are associated with nephritis, renal ischemia, urinary tract obstruction, and certain extra renal diseases. The observed nephrotoxicity brought about by

$KBrO_3$ in this study is similar to earlier observations [27]. Whereas, no remarkable changes in creatinine serum level were detected after 2 and 4 weeks. These results disagreement with many researchers that confirming the $KBrO_3$ caused increase in creatinine serum levels [24,25]. In the protected group no remarkable changes in urea and creatinine serum levels were detected after 2 weeks.

Results of the present study are in accordance with the findings of Adam *et al.* [23]. Nevertheless, no improvement was observed in protected rats' group after 4 weeks, where noted elevation in the same parameters. These increased maybe causes by acute kidney damage when given $KBrO_3$ [1,28]. In the therapeutic group, a highly significant increase in urea serum levels after 2 weeks and significant elevation after 4 weeks, this result maybe is accrued by given *R. chalepensis*. In serum levels of creatinine was no remarkable changes after 2 weeks, whereas increased after 4 weeks in the therapeutic group.

CONCLUSION

In conclusion, the administration of *R. chalepensis* oil extract against $KBrO_3$ toxicity have minimal protective effects in kidney of adult male rats.

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Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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