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Influence of ethanolic extract of strawberry leaves for abrogating bromate hazards in male rats

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Abstract

Background: Potassium bromate ($KBrO_3$) has been used widely for water disinfection, hair coloring, oxidizing agent in food, food additive in bread making process as maturing agent, and as dough conditioner for flour.

Purpose: This study was carried out to investigate the effects of two doses (150 and 300 mg/kg) of ethanolic extract of strawberry leaves on antioxidant capacity of liver, kidney and testis, thyroid hormones, and kidney function in rats treated with potassium bromate as toxic and free radical producer compound.

Study design: Forty-eight male rats were divided: group 1 served as control, group 2 treated with oral dose of strawberry leaves extract (150 mg/kg), group 3 treated with oral dose of strawberry leaves extract (300 mg/kg), group 4 treated with oral dose of potassium bromate (20 mg/kg), group 5 treated with strawberry leaves extract (150 mg/kg) and potassium bromate (20 mg/kg), and group 6 treated with strawberry leaves extract (300 mg/kg) and potassium bromate (20 mg/kg) for 4 weeks.

Methods: Determination of thiobarbituric acid reactive substance (TBARS), glutathione (GSH), and superoxide dismutase (SOD) in liver, kidney, and testis tissues. Measurements of serum total protein, albumin, urea, creatinine, free triiodothyronine (FT3), free thyroxine (FT4), and insulin.

Results: Administration of potassium bromate ($KBrO_3$) induced significant increase in TBARS; decrease in GSH and SOD in liver, kidney, and testis tissues; non-significant decrease in total protein and albumin; significant increase in serum urea, creatinine, and FT3; and significant decrease in FT4 and insulin. Administration of strawberry leaves extract showed significant improvement in some studied parameters.

Conclusion: In conclusion, the protective effect of strawberry leaves extract may be attributed to its antioxidant property.

Keywords: Strawberry leave extract, Potassium bromate, Thyroid hormones, Insulin, Kidney function, Male rats

Background

Food additives play an important role as bountiful and nutritive food supply and are carefully regulated to ensure its safety when introduced into food intended for human consumption (Abuelgasim, Omer, & Elmahdi, 2008). Potassium bromate ($KBrO_3$) has been used widely for water disinfection, hair coloring, oxidizing agent in food, food additive in bread making process as maturing agent (Kurokawa, Maekawa, Takahashi, & Hayashi, 1990), and as dough conditioner for flour (Diachenko & Warner, 2002). It is also present in hypochlorite solutions produced from bromide containing salt when it was electrolyzed (Weinberg, Delcomyn, & Unnam, 2003). The intake of potassium bromate or exposure can cause the production of reactive oxygen species in living cells and induce oxidative modification of lipids and proteins in several animal tissues (Ahmad, Amani, & Mahmood, 2014). It has been reported as a potent nephrotoxic agent that cause renal oxidative stress with reduction in renal antioxidant enzymes, toxicity, and tumor cells in rats (Ali, 2013) and also causes impairment of membrane protein activities in rats (Chipman et al., 1998).

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Potassium bromate is generated as a contaminant in drinking water due to conversion of bromide found naturally in water to bromate by ozone which is used as disinfectant (Ueno, Oishi, Sayato, & Nakamuno, 2000). Bromate was found to be genotoxic and carcinogenic (Sai, Vchiyama, Ohno, Hasegawa, & Kurokawa, 1992) while potassium bromate has been evaluated for acceptable level in flour to be consumed by man (FAO/WHO, 1992). It is also used in treating barley in beer making and for improvement of the quality of fish paste products in Japan. On the other hand, potassium bromate has harmful effects on the nutritional quality of bread by lowering vitamin A_1, B_1, B_2, E, and niacin, the main vitamins in bread (FAO/WHO, 1992 and Laba, 2003).

Thyroid hormones play an important role in regulating energy balance and metabolism of glucose and lipids (Chubb, Davis, & Davis, 2005). Thyroid hormones have a considerable impact on oxidative stress (Tejovathi et al., 2013), ascribed to their role in cellular metabolism and oxygen consumption (Peppa, Betsi, & Dimitriadis, 2011). The overproduction of reactive oxygen species (ROS) results in increased oxygen consumption by thyroid hormones which disturbs the prooxidant/antioxidant balance leading to oxidative and consequent damage to cellular structures, lipids, proteins, and DNA (Fernandez et al., 2006). Thyroid hormones are crucial to glucose homeostasis (Kim, Tull, Talbott, Vogt, & Kuller, 2002) and in contrast, insulin is the first hormone responsible for the glucose control. So there is a relation in the effect of T3 and insulin, determining lipid and glucose metabolic pathways (Lambadiari et al., 2011).

Some herbs are used to cure many diseases in traditional medicine because it is rich with natural antioxidants while other herbs possess bioactive constituents such as phenolic and polyphenolic compounds which regulate various immune systems and possess antioxidant and anti-inflammatory properties (Aruoma, 2003).

Strawberry is a widely grown hybrid species of the genus Fragaria and is a shrubby plant with big leaves and thin creeper stalks which spread and takes root on ground. All parts of this plant have medical application and have been used in various forms (Rostamian, Shakeri, & Estakhr, 2011). The leaves contain many bioactive compounds including flavonoids, ascorbic acid, tannis, and essential oils (Wang & Jiao, 2000). Ascorbic acid and flavonoids are powerful antioxidant compounds that neutralize the harmful effects associated with injury induced by reactive oxygen species (Mandave, Rani, Kuvalekar, & Ranjekar, 2013). In traditional medicine, strawberry leaves are used for treating hypocholesterolemia, an appetizer, lower blood pressure, diuretic, expel kidney stones and intestinal worms, treat anemia, hepatitis, arthritis and gastrointestinal disorders, strengthen nervous system and immune system, promote liver intestinal activity, suppress diarrhea, and speed up metabolism (Duru, 2012).

This study was carried out to investigate the effects of two doses (150 and 300 mg/kg) of ethanolic extract of strawberry leaves on antioxidant capacity of liver, kidney and testis, thyroid hormones, and kidney function in rats treated with potassium bromate as toxic and free radical producer compound.

Materials and methods

Chemicals

Potassium bromate was purchased from El-Gomhoria Company, Cairo, Egypt.

Preparation of ethanolic extract of strawberry leaves

Strawberry leaves were collected from El-Dair village, Tukh Centre, El-Qalyubia Government, Egypt. The fresh harvested leaves of strawberry plant were washed with distilled water to remove impurities such as dust and sand then dried at room temperature (25 °C). The leaves were blended to a mesh size of 1 mm. The blended sample of 1 kg was placed in 4 L of 70% ethanol for 48 h then filtered and concentrated to dryness using rotary evaporator to evaporate all the ethanol from the extract. The dry extract was kept in the refrigerator until usage and prepared the dose by dissolve it in distilled water (Japon Lujan & Luque de Castro, 2006).

Animals

Forty-eight male albino rats (140 ± 20 g) were used in the present study and obtained from the animal house of the Nuclear Research Centre, Egyptian Atomic Energy Authority. The rats were kept in plastic cages under normal conditions of temperature with 12 h light-dark cycle during the experiment. The rats were fed on standard diet and water ad libitum. The rats were randomly divided into six groups containing eight rats in each.

Experimental design

Male rats were treated orally using stomach tube as follow:

Group 1: served as control and received 1 ml distilled water.
Group 2: treated daily with oral dose of strawberry leaves extract (150 mg/kg b.wt) for 4 weeks (low dose).
Group 3: treated daily with oral dose of strawberry leaves extract (300 mg/kg b.wt) for 4 weeks (high dose).
Group 4: treated daily with oral dose of potassium bromate (20 mg/kg b.wt) for 4 weeks.
Group 5: treated daily with low oral dose of strawberry leaves extract (150 mg/kg b.wt) then after 2 h, rats were treated orally with potassium bromate (20 mg/kg b.wt) for 4 weeks.

Group 6: treated daily with high oral dose of strawberry leaves extract (300 mg/kg b.wt) then after 2 h, rats were treated orally with potassium bromate (20 mg/kg b.wt) for 4 weeks.

Blood sampling

Blood samples were collected from reto-orbital venous plexus then centrifuged at 3000 rpm for 10 min to obtain serum for biochemical analysis.

Preparation of liver, kidney, and testis homogenates

Portion of liver, one kidney, and one testis were quickly removed, washed in an ice-cold saline then blotted individually on filter paper. Every tissue was then homogenized in phosphate buffer (pH 7.4) then kept at − 20 °C for biochemical assays.

Biochemical analysis

The oxidative stress in hepatic, renal, and testicular tissues was determined as thiobarbituric acid reactive substances (TBARS) according to Yoshioka, Kawada, Shimada, and Mori (1979). Glutathione (GSH) was determined according to the method of Beutler, Duran, and Kelly (1963); this method is based on the reduction of 5,5′dithiobis (2-nitrobenzoic acid) (DTNB) with GSH to produce a yellow compound. The reduced chromogen is directly proportional to GSH concentration and its absorbance can be measured at 405 nm and superoxide dismutase (SOD) was determined by the method of Nishikimi, Roa, and Yogi (1972); this assay relies on the ability of the enzyme to inhibit the phenazine methosulphate-mediated reduction of nitroblue tetrazolium dye.

Serum total protein and albumin were determined according to Armstrong and Carr (1964) and Doumas, Waston, and Biggs (1972), respectively and serum urea and creatinine were determined according to Faukemar and King (1976) and Fawcett and Scott (1960), respectively. Free thyroxin (FT4), free triiodothyronine (FT3), and insulin were assayed by radioimmunoassay (RIA) depending on solid-phase RIA technique using kits produced by Immunotech, A Beckman Coulter Company.

Statistical analysis

Data were statistically analyzed using one-way analysis of variance (ANOVA). Differences between means of various treatments were tested using Duncan multiple range test (Duncan, 1955).

Results

Data in Table 1 showed that rats administered potassium bromate revealed significant increase ($P < 0.05$) in TBARS

Table 1 Effect of potassium bromate and/or strawberry leaves extract on TBARS, GSH, and SOD in hepatic, renal, and testicular tissues of different rat groups

Parameters	Groups					
	Control	150 mg extr.	300 mg extr.	$KBrO_3$	150 mg extr. + $KBrO_3$	300 mg extr. + $KBrO_3$
Liver						
TBARS (nmol/g wet tissue) % of change	28.58 ± 1.80^{c}	27.44 ± 1.71^{c}	27.39 ± 1.90^{c}	79.50 ± 3.37^{a}	38.36 ± 3.16^{b} − 51.74%	35.89 ± 2.07^{b} − 54.85%
GSH (mg/g wet tissue) % of change	61.53 ± 2.45^{a}	66.84 ± 1.16^{a}	67.55 ± 4.08^{a}	41.02 ± 4.27^{b}	57.99 ± 4.75^{a} + 41.37%	58.00 ± 2.86^{a} + 41.39%
SOD (U/g wet tissue) % of change	230.94 ± 8.58^{a}	234.70 ± 7.94^{a}	243.30 ± 5.69^{a}	109.37 ± 9.91^{c}	194.86 ± 9.43^{b} + 80.91%	202.38 ± 8.90^{b} + 85.04%
Kidney						
TBARS (nmol/g wet tissue) % of change	36.84 ± 1.49^{b}	36.45 ± 2.91^{b}	36.11 ± 1.48^{b}	82.07 ± 2.52^{a}	44.06 ± 4.82^{b} − 46.31%	41.99 ± 5.41^{b} − 48.84%
GSH (mg/g wet tissue) % of change	68.43 ± 2.88^{a}	68.97 ± 2.71^{a}	69.67 ± 3.02^{a}	48.92 ± 2.05^{b}	61.54 ± 2.24^{a} + 25.79%	65.78 ± 5.60^{a} + 34.46%
SOD (U/g wet tissue) % of change	222.06 ± 7.46^{a}	234.37 ± 5.69^{a}	241.77 ± 10.41^{a}	140.62 ± 6.17^{c}	188.98 ± 5.77^{b} + 34.39%	192.33 ± 10.42^{b} + 36.77%
Testis						
TBARS (nmol/ g wet tissue) % of change	28.97 ± 1.38^{b}	26.44 ± 1.65^{b}	26.37 ± 2.63^{b}	47.99 ± 1.88^{a}	34.63 ± 3.06^{b} − 27.84%	31.32 ± 2.56^{b} − 34.74%
GSH (mg/g wet tissue) % of change	86.96 ± 5.29^{ab}	89.97 ± 2.34^{a}	90.53 ± 1.61^{a}	54.46 ± 2.72^{c}	66.13 ± 3.57^{b} + 21.43%	73.20 ± 5.48^{b} + 34.41%
SOD (U/g wet tissue) % of change	325.00 ± 5.11^{a}	325.89 ± 6.12^{a}	338.84 ± 9.91^{a}	193.75 ± 4.81^{d}	267.82 ± 8.85^{b} + 38.22%c	281.55 ± 6.81^{c} + 45.31%

Data are represented as mean ± SE. $n = 8$ rats in each group
Values in the same row with different superscripts differ significantly ($P < 0.05$)
% of changes between bromate group and bromate + extract either low or high dose

level associated with significant decreases ($P < 0.05$) in GSH content and SOD activity of hepatic, renal, and testis tissues. On the other hand, treatment of rats with ethanolic extract of strawberry leaves, either low (150 mg/kg) or high (300 mg/kg) doses, markedly ameliorated the increase in TBARS level (– 51.74% and – 54.85% in hepatic tissue, – 46.31% and 48.84 in renal tissue, – 27.84% and – 34.74% in testicular tissue) and the decrease in GSH content (+ 41.37% and 41.39% in hepatic tissue, + 25.79% and + 34.46% in renal tissue, + 21.43% and + 34.41% in testicular tissue) and SOD activity in hepatic (+ 80.91% and + 85.04%), renal (+ 34.39% and + 36.77), and testis tissues (+ 38.22% and + 45.31%) as compared to bromate-treated group.

Table 2 showed that the administration of potassium bromate to rats for 4 weeks induced non-significant decrease in total protein and albumin, and significant increase ($P < 0.05$) in serum urea and creatinine. Both doses of strawberry leaves extract caused the decrease in urea level (by 15% and 17%) as well as in creatinine level (by 10% and 14%) as compared to those in the bromate alone treated group.

Table 3 showed that the levels of FT4 and insulin in $KBrO_3$-treated rats were significantly decreased ($P < 0.05$) while significant increase ($P < 0.05$) in FT3 level was recorded. On the other hand, administration of ethanolic extract of strawberry leaves, either low or high doses, can improve these parameters to be near the control level. Treated groups with bromate + extract either low or high doses of extract had % of change of FT4 level (+ 42.52% and + 46.26%), FT3level (– 25.89% and – 22.17%), and insulin level (+ 36.09% and + 43.86%) as compared to bromate group.

Discussion

The oxidative stress is produced as a result of an imbalance between reactive oxygen species and antioxidant defense system (Dwivedi & Sakar, 2010). In the present study, rats administered with potassium bromate showed significant increase in TBARS level and significant decrease in GSH concentration and SOD activity in renal, hepatic, and testicular tissues. This result is in agreement with Parsons and Chipman's report (Parsons & Chipman, 2000). Potassium bromate has the ability to cause tissue damage by the free radical mediated reactions (Omer, Abuelgasim, & Elmahdi, 2008; Watanabe, Tajima, Yamaguchi, & Fukui, 2004) and by facilitating the production of free radicals which react with some cellular components and cause oxidation of polyunsaturated fatty acids which in turn cause lipid peroxidation (Abd El-Ghany & El-Metwally, 2010). Portion of potassium bromate may be excreted in urine as bromate or bromide (Fuji et al., 1982) which will lower its level in the blood and tissues. However, the metabolism of potassium bromate is stable in the body and small amounts can be reduced to bromide by glutathione in the liver and cause the decrease in GSH level in rats administered potassium bromate (Kutom, Bazilski, Magana, & Deunea, 1990). This result is in agreement with Ahmad et al.'s finding (Ahmad, Khan, & Mahmood, 2013).

The present study showed significant amelioration in TBARS level in hepatic, renal, and testicular tissues in rats administered strawberry leaves extract before administration of potassium bromate as compared to bromate group. These results may be due to the high antioxidant capacity of strawberry leaves extract (Buřičová and Réblová (2008) due to the presence of polyphenolic compounds (Wang & Jiao, 2000) such as tannins, flavonoids, and ascorbic acid (Duru, 2012).

The non-significant decrease in total protein and albumin in rats administered potassium bromate may be due to normal protein synthesis. These results are in agreement with Khan, Khan, and Sahreen (2012) and Stuti and D'Souza's (2013) reports. The rats treated with potassium bromate showed significant increase in urea and creatinine which reflects renal injuries induced by

Table 2 Effect of potassium bromate and/or strawberry leaves extract on serum total protein, albumin, urea and creatinine levels of different rat groups

Parameters	Groups					
	Control	150 mg extr.	300 mg extr.	$KBrO_3$	150 mg extr. + $KBrO_3$	300 mg extr. + $KBrO_3$
Total protein (g/dl) % of change	6.10 ± 0.35^a	6.12 ± 0.42^a	6.14 ± 0.38^a	5.15 ± 0.25^a	5.61 ± 0.14^a + 8.93%	5.72 ± 0.16^a + 11.07%
Albumin (mg/dl) % of change	4.58 ± 0.32^a	4.65 ± 0.31^a	4.74 ± 0.37^a	3.84 ± 0.24^a	3.99 ± 0.25^a + 3.91%	4.11 ± 0.27^a + 7.03%
Urea (mg/dl) % of change	39.98 ± 1.46^c	39.37 ± 1.16^c	39.87 ± 2.13^c	54.34 ± 1.31^a	46.21 ± 1.63^b – 14.96%	44.86 ± 2.46^b – 17.45%
Creatinine (mg/dl) % of change	0.68 ± 0.02^c	0.62 ± 0.07^c	0.61 ± 0.04^c	0.92 ± 0.05^a	0.83 ± 0.02^b – 9.78%	0.79 ± 0.03^b – 14.13%

Data are represented as mean ± SE. $n = 8$ rats in each group
Values in the same row with different superscripts differ significantly ($P < 0.05$)
% of changes between bromate group and bromate + extract either low or high dose

Table 3 Effect of potassium bromate and/or strawberry leaves extract on serum free thyroxin (FT4), free triiodothyronine (FT3) and insulin levels of different rat groups

Parameters	Groups					
	Control	150 mg extr.	300 mg extr.	$KBrO_3$	150 mg extr. + $KBrO_3$	300 mg extr. + $KBrO_3$
FT4 (ng/dl) % of change	3.27 ± 0.45^{a}	3.91 ± 0.33^{a}	3.39 ± 0.48^{a}	2.14 ± 0.19^{b}	3.05 ± 0.31^{a} + 42.52%	3.13 ± 0.39^{a} + 46.26%
FT3 (pg/ml) % of change	4.33 ± 0.26^{b}	4.64 ± 0.28^{b}	4.29 ± 0.25^{b}	5.91 ± 0.26^{a}	4.38 ± 0.26^{b} − 25.89%	4.60 ± 0.51^{b} − 22.17%
Insulin (ng/L) % of change	17.70 ± 0.65^{a}	18.62 ± 1.23^{a}	19.49 ± 0.79^{a}	9.53 ± 0.27^{b}	12.97 ± 0.64^{cb} + 36.09%	13.71 ± 1.04^{b} + 43.86%

Data are represented as mean ± SE. $n = 8$ rats in each group
Values in the same row with different superscripts differ significantly ($P < 0.05$)
% of changes between bromate group and bromate + extract either low or high dose

$KBrO_3$. Albuminuria, proteinuria, creatinine, and urea are considered as renal function markers in nephrotoxicity (Ahmad & Mahmood, 2014; Ibrahim & Abd El-Maksoud, 2015; Zou et al., 2014).

In this study, rats treated with ethanolic extract of strawberry leaves before administration of potassium bromate showed elevated serum protein and albumin, and decrease in urea and creatinine. This result indicate the activity of strawberry leaves extract to ameliorate renal function in potassium bromate-treated rats due to its antioxidant compounds; flavonoids and ellagic acid (Hannum, 2004). The activity of phenolic compounds may be related to its antioxidant effects and due to their ability to scavenge free radicals through the presence of hydroxyl groups in these compounds (Djeridane et al., 2006).

In the present study, rats administered potassium bromate showed significant decrease in free thyroxin (FT4) and significant increase in free triiodothyronine (FT3) due to degeneration of the follicular cells as well as decrease in insulin level. The chronic administration of $KBrO_3$ may cause thyroid and mesothelioma tumors in rats (Wolf et al., 1998). Our results demonstrate beneficial effect of the extract tested on insulin level which is in accordance with Ibrahim and Abd El-Maksoud's (2015) findings who reported the increase in serum insulin level in diabetic rats treated with strawberry leaves extract.

Conclusion

The present study showed improvement in renal function, insulin, and free thyroid hormones after administration of two doses of ethanolic extract of strawberry leaves (150 and 300 mg/kg) in potassium bromate-treated rats. These improvements were more pronounced in the high dose (300 mg/kg) than that of the low dose (150 mg/kg) of strawberry leaves extract due to the antioxidant activity of such extract.

Abbreviations

ANOVA: One-way analysis of variance; FT3: Free triiodothyronine; FT4: Free thyroxin; GSH: Glutathione; $KBrO_3$: Potassium bromated; RIA: Radioimmunoassay; SOD: Superoxide dismutase; TBARS: Thiobarbituric acid reactive substance

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Availability of data and materials

All data sets, on which the conclusions of the manuscript rely on, are present in the results section in the manuscript.

Authors' contributions

The authors NEM and SEA designed the study plan and supervised all parts of this study. SEA prepared the strawberry leaves extract. NEM performed the experiment, wrote the manuscript, and analyzed the data and NEM and SEA interpreted the results of the experiment and NEM did the final edition of the manuscript. All the authors read and approved the final manuscript.

Ethics approval

The study was carried out at the Nuclear Research Centre, Egyptian Atomic Energy Authority. The manuscript was approved by the scientific committee of publication, committee No. (164) of the Egyptian Atomic Energy Authority. All rats were handled in accordance with the standard guide for the care and use of laboratory animals Published by The US National Institutes of Health (NIH publication No85-23, 1996).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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