Journal of Pharmacological Reports

Starek, Starek-Swiechowicz, J Pharma Reports
2016, 1:3

Review Article Open Access

Toxicological Properties of Potassium Bromate

Andrzej Starek* **and Beata Starek-Świechowicz**

Department of Biochemical Toxicology, Chair of Toxicology, Medical College, Jagiellonian Uniwersity, Kraków, Poland

***Corresponding author:** Andrzej Starek, Department of Biochemical Toxicology, Chair of Toxicology, Medical College, Jagiellonian Uniwersity, Kraków, Poland, Tel: +48 12 422 10 33; E-mail: mfstarek@cyf-kr.edu.pl

Received date: May 30, 2016; **Accepted date:** July 12, 2016; **Published date:** July 15, 2016

Abstract

Potassium bromate ($KBrO_3$), used in both the food and cosmetics industry, and a drinking water disinfection by-product, is a nephrotoxic chemical and rodent carcinogen. As $KBrO_3$ is primarily an oxidizing compound, reactive oxygen and other species generated from bromate have been held responsible for the genotoxic, carcinogenic and toxic effects. Bromate induces primary DNA oxidative damage, mutations, and DNA-strand breakage, structural chromosomal aberration types of chromatid breaks and exchanges. $KBrO_3$ induces of micronuclei in different cells *in vivo*. Bromate is clastogenic agent. Bromate administered in the drinking water was tumorogenic in the rat kidney, thyroid, and mesothelium and was a renal carcinogen in the male mouse. The incidence of mesotheliomas on the tunica vaginalis testis in rats was a dose-dependent manner. It was shown that $KBrO_3$ is an effective promoter of kidney neoplasia induced by N-ethyl-N-hydroxyethylnitrosamine. There are a lot naturally occurring compounds which may be used as effective chemopreventive agents against $KBrO_3$-mediated renal and other organ oxidative stress, toxicity and tumor promotion response.

Keywords: Potassium bromate; Oxidative damages; Genotoxicity; Carcinogenicity; Chemoprotection

Introduction

Potassium bromate ($KBrO_3$; CAS No. 7758-01-2) is not a naturally occurring compound, but is synthesied by passing bromine vapour through a solution of potassium hydroxide when heated. This compound exists as white crystals, crystalline powder or granules. It is highly soluble in water (75 g/L at 25°C), slightly soluble in ethanol; it is very stable in water solution at room temperature. $KBrO_3$ decomposes at temperature above 370°C, with the emission of oxygen and toxic fumes [1].

$KBrO_3$ is a strong oxidizing agent that has been used in flour milling, as an ingredient in fish-paste in Japan, in cheese making, in beer malting, and as a component of cold hair-wave liquids, and a oxidizing compound [1].

Moreover, bromate is formed as a by-product of water disinfection by ozonation and is frequently detected in top and bottled water. In fact bromate is one of the most prevalent disinfection by-product of surface water [2].

Ozone has been introduced for water disinfection because it is more efficient than chlorine for killing microbes and leads to much lower levels of carcinogenic trihalomethanes (THMs). Ozone leads to formation of hydrobromous acid in water with high bromine content and forms brominated organic by-products and bromate [3]. Occupational exposure to $KBrO_3$ occurs mainly in production plants during packaging processes.

Toxicity in humans

In Western countries most poison cases with $KBrO_3$ were by accidental ingestion, mainly among children. In Japan, $KBrO_3$ was more often ingested for tentative suicide by young women, especially hairdressers [1]. The lethal dose of this chemical in man has been estimated at 5-500 mg/kg of body weight (b.w.) [4,5]. In reported cases nine out of twenty four adults died 3-5 days after ingestion [5].

In the acute phase of poisoning, vomiting and diarrhea with abdominal pain were the main symptoms. Subsequent manifestations included oliguria, anuria, deafness, thrombocytopenia, hypotension, vertigo, and depression of the central nervous system. Acute renal failure was associated with hemolytic uremic syndrome [4]. In both children and adults, oliguria and death from renal failure were seen [4].

In biopsy of the kidney atrophy, necrosis, degeneration, and regeneration of the proximal tubular epithelim have often been observed. In the later stages, sclerosis of the glomeruli and interstitial fibrosis have been reported. Cardiotoxicity and hepatotoxicity have also been observed [5].

Partial hearing loss and complete deafness have also been reported [4,6]. Severe irreversible sensorineural hearing loss within 4-16 h of bromate ingestion was recorded in almost all of the cases. Moreover, strong irritating action of $KBrO_3$ on gastric mucosa was noted [6,7]. The signs and symptoms of chronic intoxication of humans by $KBrO_3$ have not been described.

Toxicity in experimental animals

The values of median lethal doses (LD_{50}) per os of $KBrO_3$ in rats, mice, and hamsters (Table 1) were comprised the range of 280 to 495 mg/kg of body weight [1]. Other data indicate that the oral LD50 value of this compound in rats, determined by OECD Guideline 401 method, was estimated at level of 157 mg/kg b.w. Potassium bromate has been classified as a compound belonging to the category "Toxic" [8].

Major toxic signs and symptoms after a single intragastric administration of $KBrO_3$ were tachypnoea, hypotermia, diarrhea,

lacrimation, piloerection, suppression of locomotor movement, ataxic gait, and animals lying in a prone position. At autopsy the major findings were strong hyperemia of the glandular stomach mucosa and congestion of the lung. Microscopically, epithelial dilatation and desquamation of the distal convoluted tubules were observed in rats 1 h after $KBrO_3$ administration. Necrosis and degenerative changes of the proximal tubular epithelium were noted after 3 h and regenerative alterations of the tubular epithelium occured within 48 h. In mice and hamsters, however, these histopatological changes were later observed and to a lesser intensity [1]. A nephrotoxic single dose of $KBrO_3$ (100 mg/kg b.w.) administered to rats resulted in a decline in the specific activities of leucine aminopeptidase (LAP), γ-glutamyl transferase (γ-GT), maltase, and alkaline phosphatase (AP), enzymes of brush border membrane (BBM), and also induced oxidative stress in kidney. The enzymes of carbohydrate metabolism, i.e., lactate dehydrogenase, malate dehydrogenase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, and fructose-1,6-bisphosphatase were also altered and suggest a shift in energy metabolism from the aerobic to anaerobic mode. Maximum changes in all the parameters were 48 h after administration of $KBrO_3$, after which recovery took place [9].

Species/Strain	Male	Female
Rat F344	400 (348-460)[a]	495 (446-549)
Rat Wistar	157	157
Mouse B6C3F1	280 (250-314)	355 (311-405)
Mouse MS/Ae	471	-
Mouse CD-1	289	-
Hamster Syrian golden	388 (318-473)	460 (400-529)

Table 1: LD_{50} (mg/kg b.w.) values in rat, mouse, and hamster after p.o. administration [1,8]. [a]Numbers in parentheses are 95% confidence limits. Observation time amounted 7 days.

In the same experiment similar effects were observed in the intestinal mucosa [10]. $KBrO_3$ administered to rats resulted in increased lipid peroxidation, protein oxidation, hydrogen peroxide levels and decreased the reduced glutathione (GSH) content indicating the induction of oxidative stress in blood. Methemoglobin levels, methemoglobin reductase activity, and nitric oxide concentrations were significantly increased while the total anti-oxidant power and vitamin C concentration were decreased [11].

The chronic effects of $KBrO_3$ administered via drinking water or by feeding animals with bread treated with the compound were observed. In male Fischer 344 (F344/N) rats exposed to $KBrO_3$ in drinking water at dose levels of 0, 1.5, 7.9, 16.9, and 37.5 mg/kg-day for up to 100 weeks were found non-neoplastic alterations of treatment-related increases in hyperplasia of the transitional cells of the renal papilla and pelvis, which termed urothelial hyperplasia. This effect at and above 7.9 mg/kg-day $KBrO_3$ was reported, with the no-observed-adverse-effect level (NOAEL) of 1.5 mg/kg-day. In rats administered only with 37.5 mg/kg-day weights significant increases in the kidney and thyroid weights and elevated relative liver, kidney, thyroid, and spleen weights were seen [12,13].

Male F344 rats were treated with $KBrO_3$ in drinking water at dose of 0, 0.4, 1.6, 8.1, 16.2, and 32.4 mg/kg-day for 2 or 13 weeks. Increases in kidney weights were observed in rats of at the highest dose (32.4 mg/kg-day) group following 2- and 13-weeks exposure. In renal tubules of rats exposed to 16.2 and 32.4 mg/kg-day of $KBrO_3$ for 2 weeks and in rats of the 32.4 mg/kg-day group at 13 weeks hyaline droplets were seen. A no observed effect level (NOEL) of 8.1 mg/kg-day was selected on the base of the absence of microscopic alterations in the kidney [14].

Eighteen rats, three dogs, and three monkeys were fed a diet containing 84% flour treated with $KBrO_3$ at a level of 75 mg/kg for a period of 4, 12 and 8 weeks respectively. No adverse effects were found in any of the species. Twelve rats and two dogs were fed with bread made from flour containing 200 mg/kg $KBrO_3$ for 16 days, and three dogs given diets containing flour treated with 70 mg/kg $KBrO_3$ for 6 weeks, and also four dogs were given bread made from flour containing 200 mg/kg $KBrO_3$ for 17 months showed no adverse effects associated with the intake diets [15].

Mutagenicity and genotoxicity

No data were available on the subject of mutagenicity and genotoxicity in humans. Potassium bromate was found to be weakly mutagenic in *Salmonella typhimurium* TA100 at a concentration of 3 mg/plate after metabolic activation. However, the compound proved not mutagenic active in *S. typhimurium* TA98, TA1535, TA1537, TA1538, *Escherichia coli* WP2try- and *E. coli* WP2try-his- with or without metabolic activation [16,17]. $KBrO_3$ was also mutagenic in *S. typhimurium* TA102 and TA104, strains which are sensitive to chemicals that generate reactive oxygen species (ROS) and active oxygen radicals [18].

Potassium bromate as a strong oxidant induces primary DNA oxidative damage. $KBrO_3$ increases 8-hydroxydeoxyguanosine (8-OH-dG) DNA adduct levels, a representative marker of oxidative DNA modification, *in vivo* and *in vitro* [19-21]. Under cell-free conditions, no modification was induced by $KBrO_3$ alone, but evident DNA damage was seen in the presence of reduced glutathione (GSH). In L1210 mouse leukemia cells and LLC-PK1 porcine kidney cells, $KBrO_3$ led to a DNA damage profile similar to that observed after treatment of cell-free DNA with bromate and GSH [22]. Speit et al. [23], using the Comet assay in V79 Chinese hamster cells treated with $KBrO_3$, found that this chemical significantly increased levels of 8-OHdG. They observed four Hprt point mutations and three of them were G:C to T:A transversions which usually arise after replication of 8-OHdG. The induction of DNA breakage was confirmed in the other studies [24,25]. Oxygen radicals can damage bases in DNA to result in double-strand breakage. $KBrO_3$ induced DNA-strand breakage in V79 cells, human leucocytes and rat kidney epithelial cells [23,26].

Double-strand breaks occurring spontaneously or caused by DNA-demaging agents are repaired in mammalian cells through recombinational repair or end rejoining. Recombinational repair involves filling DNA gaps with homologous sequences existing on homologous chromosomes or sister chromatids, whereas end rejoining joins the ends of the two broken strands in a nonhomologous fashion [27]. Both of these repair mechanisms could lead to loss of heterozygosity (LOH) produced by deletion, recombination or other chromosomal alteration. LOH is considered to be involved with the initiation and promotion of cancer because it is an important mechanism in the inactivation of autosomal genes. Mutations in tumor suppressor genes are generally recessive. A mutation in several alleles of the tumor suppressor gene disturbs growth control of cell and is a crucial in the development of cancer [28].

Potassium bromate is a strong, dose-related mutagen in the Thymidine kinase gene of L5178Y/$Tk^{+/-}$ -3.7.2C mouse lymphoma cells. This compound induced very high mutant frquencies, reaching about 1400×10^{-6} at the highest concentration (3 mM) [28]. This is in contrast to the relatively weak mutagenic activity demonstrated in the Hprt mutation assay and the microbal mutation assays. The mutant frequencies induced by $KBrO_3$ in the Hprt gene of V79 Chinese hamster cells reached 4, 7, 30 and 72×10^{-6} at the concentration 0, 5, 10 and 20 mM, respectively [23]. Thus, the mutant frequency caused by $KBrO_3$ in the Tk gene of mouse lymphoma cells is over 200 times higher than that in the Hprt gene of V79 cells at comparable concentrations. The large difference in these results are probable related to the potent clastogenicity of bromate. Chemicals acting mainly by a clastogenic mechanism induce detectable mutagenicity in the Tk gene but are weakly mutagenic or nonmutagenic in the Hprt gene and in microbal assays [29].

Structural chromosomal aberrations in Chinese hamster lung cells treated with $KBrO_3$ *in vitro* at doses of 0.0625-0.250 mg/mL, without metabolic activation, and in bone marrow cells of male Long-Evans rats after administration this chemical at doses of 250.5 mg/kg i.p. or 344.0 mg/kg p.o. were observed [16,17,30]. The main aberration types observed were chromatid breaks and chromatid exchances. The clastogenic activity of $KBrO_3$ was considered to be relatively strong [1].

Potassium bromate induced of micronuclei in polychromatic erythrocytes in male ddY mice in a dose-dependent manner when it was administered at doses higher than 25 and 100 mg/kg b.w. by i.p. and p.o. routes, respectively, was found [31]. Similar effects were seen in peripheral blood reticulocytes of CD-1 and ddY mice, and F344 rats [32-34], and also in the cells of glandular part of stomach and liver of rats treated with $KBrO_3$ p.o. at dose of 40-80 mg/kg b.w. for 4, 14, and 28 days [35]. In other study conducted on male mice Ms/Ae and CD-1, administration of $KBrO_3$ at doses of 18.8-150 mg/kg b.w. i.p. or 37.5-300 mg/kg b.w. p.o., respectively, led to an increase in a dose-dependent manner in micronuclei in bone marrow polychromatic erythrocytes. In mice CD-1 observed effect was more pronounced after chemical administration i.p. than p.o. [36].

It has been sugested that oxidative DNA damage can cause mutations that contribute to the activation of oncogenes and/or the inactivation of suppressor genes, thereby leading to tumorigenesis [37].

Carcinogenicity

No data were available on the subject of carcinogenicity in humans. Potassium bromate is a rodent carcinogen. It is possibly carcinogenic to humans (Group 2B) [1,38].

Male and female F344 rats developed renal cell tumors and thyroid follicular tumors, and the male rats had also an increased incidence of abdominal mesotheliomas [12,13,39,40]. DeAngelo et al. [12] demonstrated that $KBrO_3$ is carcinogenic in the rat kidney, thyroid, and mesothelium and that it is a renal carcinogen in the male B6C3F1 mouse. $KBrO_3$ was carcinogenic in rats at water concentrations as low as 20 mg/L and dose of 1.5 mg/kg-day [12].

F344 rats of both sexes were given $KBrO_3$ in drinking water at concentrations of 250 and 500 mg/L for 110 weeks. Daily intakes of this compound amounted 12.5 and 27.7 mg/kg-day in males and 12.5 and 25.5 mg/kg-day in females in the high- and low-dose groups, respectively. All dosed groups of rats had statistically significant high incidences of renal cell tumors (RCT), dysplastic foci (DF), which are preneoplastic lesions for RCT, and also adenocarcinomas, and adenomas. Other tumors found in the kidney were two transitional cell papillomas, two transitional cell carcinomas, and one angiosarcoma in treated rats and one liposarcoma in a control rat [40]. The renal cell tumors in rats are morphologically similar to human renal cell cancer of the clear-cell type [13]. In male rats given 250 or 500 mg/L $KBrO_3$ also occurred mesotheliomas of the peritoneum at a significantly higher incidence than in the controls. On the other hand, no mesotheliomas were observed in treated and control female rats [40] (Table 2).

Group $KBrO_3$ (mg/L)	Number of rats[a]	Mean induction time ± SD, week	Number of rats (%) bearing			
			DF	RCT	Adeno-carcinomas	Adenomas
Male						
0	52	111.0 ± 0.0	6(11)	3(6)	3(6)	0(0)
250	53	103.7 ± 9.1	32(60)**	32(60)**	24(45)**	10(19)*
500	53	88.9 ± 18.9	40(77)**	46(88)**	44(85)**	5(10)*
Female						
0	47	-	0(0)	0(0)	0(0)	0(0)
250	50	107.6 ± 5.8	13(25)*	28(56)**	21(40)**	8(15)*
500	49	107.9 ± 5.6	9(173)*	39(80)**	36(69)**	9(17)*

Table 2: Incidences of renal cell tumors (RCT), dysplastic foci, and other neoplastic changes in F344 rats given $KBrO_3$ in drinking water [40]. [a]Males and females which survived longer than 14 and 85 weeks, when the earliest RCTs were found, *p ≤ 0.01 when compared with controls, **p ≤ 0.001 when compared with controls.

In the other study F344 male rats were treated with 0, 15, 30, 60, 125, 250 or 500 mg/L $KBrO_3$ in drinking water for 104 weeks. The mean survival time of the animals treated with 500 mg/L (82.8 weeks) was significantly shorter than that of controls (103.1 weeks). In all exposed groups the rats had RCT, but there were statistically significant increases only at doses of ≥125 mg/L. The incidences of

renal adenomas and RTC were significantly elevated in rats receiving concentrations of 125, 250, and 500 mg/L.

Also, significant dose-related increases in the incidences of DF were observed in all groups exposed to concentrations over 30 mg/L. Follicular adenomas and adenocarcinomas of the thyroid were seen in the groups treated with 60, 250, and 500 mg/L. In the rats of the 500 mg/L dose group the combined incidences of benign and malignant follicular alterations were significantly increased. Mesotheliomas of the peritoneum were significantly elevated in animals receiving 500 mg/L (Table 3) [41].

Group $KBrO_3$ (mg/L)	Number of rats (%) bearing/Effective number of rats				
	Renal adenocarcinomas	Renal adenomas	Peritoneal mesotheliomas	Thyroid adenocarcinomas	Thyroid adenomas
0	0/19	0/19	0/19	0/19	0/19
15	0/19	0/19	0/19	0/19	0/19
30	0/20	0/20	3/20(15)	0/20	0/20
60	0/24	1/24(4)	4/24(17)	0/24	1/24(4)
125	0/2	5/24(21)*	2/24(8)	0/24	0/24
250	0/20	5/20(25)*	3/20(15)	1/20(5)	2/20(10)
500	3/20(15)	6/20(30)*	15/20(75)**	2/20(10)	5/20(25)*

Table 3: Incidences of renal tumors, thyroid tumors and mesotheliomas in male F344 rats in the dose-response study [41]. *$p \leq 0.05$ when compared with control, **$p \leq 0.001$ when compared with control.

The carcinogenicity of $KBrO_3$ was studied also in male B6C3F1 mice and male F344/N rats, which were treated with 0, 9.1, 42.4 and 77.8 mg/kg-day, and 0, 1.5, 7.9, 16.9, and 37.5 mg/kg-day, respectively. $KBrO_3$ was administered in the drinking water for up to 100 weeks. This study showed that $KBrO_3$ is carcinogenic in the rat kidney, thyroid, and mesothelium and is a renal carcinogen in the male mouse. There was a treatment, but not a dose-related increase in the incidence of mouse renal tumors after 100 weeks of $KBrO_3$ intake in the drinking water. A dose-dependent increased incidence of mesotheliomas on the tunica vaginalis testis was seen in exposed groups (Table 4). In many affected rats, mesothelioma was also present on the serosal surface of some or all of the abdominal viscera and the mesentery. In all rats with mesotheliomas on the abdominal viscera, there were also mesotheliomas of the vaginal tunic. Rats treated with $KBrO_3$ at dose of 37.5 mg/kg-day for up to 100 weeks had an increase in renal adenoma and carcinoma incidences. Most of the tumors occured in the cortex, with a few extending into the outer medulla. Rats exposed to $KBrO_3$ at dose of ≥16.9 mg/kg-day had an increased incidence of thyroid follicular proliferative changes, including hyperplasia, adenoma, and carcinoma [12].

Dose (mg/kg-day)	Number of examined rats	Number (%) of affected rats
0	47	0
1.5	49	4(8.2)
7.9	49	5(10.2)*
16.9	47	10(21.3)**
37.5	43	27(62.8)**,***

Table 4: Incidence of mesotheliomas on the tunica vaginalis testis in $KBrO_3$-treated male F344 rats [12], *$p \leq 0.05$ when compared with control, **$p \leq 0.002$ when compared with control, ***$p \leq 0.002$ (significant trend).

Although the carcinogenicity of $KBrO_3$ in rats was definitely established by several experimenters, it was thought necessary to test the promoting properties of this chemical. In the experiments N-ethyl-N-hydroxyethylnitrosamine (EHEN) was used as initiator, because this carcinogen is known as a potent initiator useful for assessing the promotion potential of exogenous compounds on kidney and liver neoplasia. In male F344 rats pre-treated with EHEN at concentrations of 500 and 1000 mg/L in drinking water for 2 weeks and then exposed to 500 mg/L $KBrO_3$ orally for the following 24 weeks were significantly increased incidences of both DF/cm^2 and RCT/cm^2 in kidney as compared to animals treated with EHEN alone. Therefore these findins clearly demonstrated enhancing activity of bromate on kidney lesion development [1]. In the other study the mean numbers of DF/cm^2 were found to be significantly increased in a dose-related manner in rats exposed to >30 mg/L $KBrO_3$. It was shown that threshold of the promoting effect of $KBrO_3$ in drinking water exists at range concentrations of 15-30 mg/L. The promoting effect of potassium bromide (KBr) was also tested since $KBrO_3$ is thermically easily degraded to KBr during the baking process. No promoting effect was observed with KBr [42].

Bromate is thought to induce its toxic and carcinogenic responses through oxidative damage resulting from increased levels of lipid peroxide [43]. Bromate forms oxigen radicals, which are known to damage DNA, as evidenced by increased 8-OHdG levels in response to oxidative stress [21,44]. Bromate must undergo cellular metabolism to cause DNA damage because DNA damage did not occur directly in mixture of DNA and bromate *in vitro* [1]. The mechanism of bromate-induced carcinogenesis may include lipid peroxidation, which generates oxygen radicals that cause DNA damage [1]. The apparent species differences in the induction of renal cell tumors are correlated with the different levels of lipid peroxidation (LPO) [21]. LPO not only act as intermediates for free radical chain reactions, but also generate

various reactive products, such as malondialdehyde and trans-4-hydroxy-2-nonenal, which directly form exocyclic DNA adducts [45,46]. A single exposure of male rats to $KBrO_3$ at high doses by i.g. intubation or by single i.p. injection causes an increase of thiobarbituric acid-reactive substances (TBARS) along with 8-OHdG formation [47,48]. However, exposure to carcinogenic doses in the drinking water failed to increase TBARS, in spite of the increase of 8-OHdG. These results suggest that DNA oxidation induced by $KBrO_3$ may occur independently of lipid peroxidation and more than 250 mg/L this compound in the drinking water can exert a carcinogenic effect by way of oxidative stress [48]. It has been reported that reduction of $KBrO_3$ by GSH and cysteine results in the generation of bromine oxides and short lived bromine radicals acting as reactive intermediates which can effectively oxidize guanine [49]. The participation of oxidative stress among possible causative factors in $KBrO_3$-induced carcinogenesis is of importance from the perspective of human health protection.

In two-stage model carcinogenesis using EHEN as an initiator, $KBrO_3$ enhanced renal carcinogenesis in both male and female rats [42,50]. Also, short-term exposure to $KBrO_3$ in males led to significantly an increase in bromodeoxyuridine-labeling indices (BrdU) in proximal convoluted tubules (PCTs) in the same dose-dependent manner as evidenced in the promotion assay [51]. Moreover, this compound induced renal ornithine decarboxylase (ODC) activity and led to [3H] thymidine incorporation in renal DNA with concomitant renal damage. Both indices are the characteristic changes of proliferative response [52]. As a possible mode of action, it was proposed involvement of α_{2u}-globulin accumulation in $KBrO_3$-induced cell proliferation in males [48]. The fact that BrdU in PCT of females exposed to $KBrO_3$ were also increased, albeit at higher doses than in males, implies the existence of other causative factors. On the ground of the results of other study it was concluded that oxidative stress generated by $KBrO_3$ might take part in induction of cell proliferation in PCT of female rats, leading to tumor promoting potential. In males, however, α_{2u}-globulin accumulation independent of oxidative stress plays a major role in cell proliferation [53].

In genetic study, the gene expression in kidneys from male F344 rats, chronically exposed to $KBrO_3$ at a non-carcinogenic (20 mg/L) and carcinogenic concentration (400 mg/L), was investigated. At high dose it was found alterations of gene transcripts involved in oxidative stress, lipid metabolism, kidney function/ion transport, and cellular function. The data obtained indicate that carcinogenic dose of $KBrO_3$ showed marked gene expression differences from the non-carcinogenic dose. Comparison of kidney development gene expression showed that the adenoma patterns are more characteristic of embryonic than adult kidneys. Moreover, the high dose kidney gene expression resemble an adenoma-like expression pattern [54].

The study on a gene expression profiles in the TK6 human lymphoblastoid cells treated with $KBrO_3$ *in vitro* revealed up-regulation of some genes involved in oxidative stress, apoptosis, and DNA repair [55]. The gene expression pattern of immortalized rat peritoneal mesothelial cells after 4 or 12 h exposure to $KBrO_3$ *in vitro* indicated oxidative stress, mitotic arrest, and apoptosis in treated cells. Increases occurred in oxidative stress responsive genes (among other heme oxygenase-1, quinone reductase, HPSP70, growth arrest and DNA damage protein 45 and 153, and p21); transcriptional regulators c-jun, c-fos, jun B, c-myc, and IκB; protein repair components; DNA repair components; lipid peroxide excision enzyme phospholipase A_2; and apoptogenic components tumor necrosis factor α, inducible nitric oxide synthase and fas-ligand. Decreases occured in bcl-2 (antiapoptotic) bax α, bad, and bok (proapoptotic) and cell cycle control elements (cyclines). Cyclin G and p14/cyclin-dependent kinase inhibitor 4b (which inhibit entry into cell cycle) were increased. Numerous signal transduction, cell membrane transport, membrane-associated receptor, and fatty acid biosynthesis and repair components were altered. As a model for $KBrO_3$-induced carcinogenicity in rat mesothelium has been proposed: $KBrO_3$ generates a redox signal that activates p53 gene and lead to transcriptional activation of oxidative stress and repair genes, dysregulation of growth control, and defective DNA repair and than results in carcinogenic process [56].

Toxicokinetics

Potassium bromate is absorbed rapidly from the gastrointestinal tract and excreted in the urine as parent compound (30% of dose) and bromide in male rats 24 h after administration. The levels of bromide were increased significantly in the plasma, red blood cells, kidney, pancreas, stomach, small intestine, and urine after intragastrically administration of $KBrO_3$. Dose-response studies revealed that in the urine of rats treated with $KBrO_3$ at doses higher than 5 mg/kg b.w. a dose-related increase in the levels of bromate. In the stomach and plasma the levels of bromate apparently decreased, whereas in small intestine and bladder initially increased (for first hour) and then decreased [57].

Following a single oral dose of $KBrO_3$ labeled by oxygen-18 (^{18}O) at dose of 25 mg/kg b.w. detectable levels of the isotopic marker were found in kidney and thyroid as target, and also in liver and testis as non-target rat organs. The levels of ^{18}O increased with time in all tissues examined. Kidney and liver had the highest levels while thyroid and testes had the least. The levels of ^{18}O were also dose-dependent and observed to be statistically increased in the kidney at doses of 10 mg/kg b.w. and higher [58].

Potassium bromate as a strong oxidizer is effectively reduced to bromide by means thiol compounds such as GSH, cysteine, and ergothioneine. This metabolic process with participation of GSH is a near stoichiometric. Rat liver and kidney homogenates and red blood cells showed strong activity for biodegradation of bromate when incubated at 37°C for 3 min. or at 100°C for 5 min. These data indicate that $KBrO_3$ biodegradation is non-enzymatic process. Moreover, bromide is yielded in the GSH-mediated reaction that corresponds well to the fact that bromide concentration increased in organs and urine of rats after an oral bromate administration [59].

Chemoprotective effects of antioxidants

Recently called attention to possibility production of bromine radicals (Br^{*}) or oxide radicals ($BrO^{\cdot}$ and $BrO_2^{\cdot}$) which likely are the species responsible for the cellular and cell-free DNA damage [22,26,60]. Chemoprotective effects of antioxidants against $KBrO_3$-induced tissue oxidative damages.

There are a lot edible plants and several compounds acting as antioxidants. Various recent studies have shown the inhibitory effect of plant constituents on $KBrO_3$ induced oxidative damage in tissues and cancer.

Nigella sativa Linn, commonly known as black cumin, is a very common ingredient of the diet and is used as a condiment of food. It is used in food for flavour, aroma and fragrance. The herb has many medical properties in traditional medicine. It is useful among other in

puerperal fever, boils, cough, rheumatism and inflammation. The aerial part of the plant contains biological active components, such as carvone, d-limonene, cymene, and a carbonyl compound, nigellone isolated from the volatile oil fraction [61].

Female Wistar rats were pretreated with Nigella sativa extract by gavage once daily for 5 days and than received a single i.p. injection of $KBrO_3$ at a dose of 125 mg/kg b.w. The effect of prophylactic treatment of rats with Nigella sativa extract resulted in a significant decrease in renal microsomal lipid peroxydation, γ-GT, H_2O_2 and xanthine oxidase activity as compared with animals given $KBrO_3$ alone. There was significant recovery of renal glutathione level and glutathione metabolizing enzymes and antioxidant enzymes. There was also reversal in the enhancement of renal ODC activity and DNA synthesis. These data suggest that Nigella sativa is a potent chemopreventive agent and may suppress renal oxidative stress, toxicity and tumor promotion response to $KBrO_3$ in rats [61].

Tephrosia purpurea is a polymorphic perennial herb occuring on the Indian subcontinent. It is used in the treatment of several diseases such as fever, chronic diarrea, asthma, tympanitis, heumatism and inflamation. It has hepatoprotective properties, and is used as a purifier of blood and is applied externally on leprosy and skin eruptions [62].

Prophylactic treatment of the rats with *T. purpurea* extract at doses of 5 mg/kg b.w. and 10 mg/kg b.w. prevented N-diethylnitrosamine-initiated and $KBrO_3$ promoted renal oxidative stress and toxicity. The depleted levels of glutathione, the inhibited activities of antioxidant enzymes, phase II metabolizing enzymes and the enhanced levels of serum creatinine and blood urea nitrogen (BUN) were recovered to a significant level. The susceptibility of renal microsomal membrane for lipid peroxidation and xanthine oxidase activity were significantly reduced. All the antioxidant enzymes were recovered dose-dependently. These data indicate that *T. purpurea* extract can be a potent chemopreventive agent against renal oxidative stress and carcinogenesis induced by N-diethylnitrosamine and bromate [63].

Similar effects were observed in the same experiment on rats pretreatment with soy isoflavones (the mixture of genistin 20 mg, daidzin 5.4 mg, and glycitin 4.6 mg, plus saponins and proteins found naturally in soy) by gavage once daily for 5 days at a dose of 5 mg/kg b.w. or 10 mg/kg b.w. and then administered with a single i.p. injection of $KBrO_3$ at a dose of 125 mg/kg b.w. Treatment of rats with soy isoflavones resulted in a significant decrease in xanthine oxidase activity as a pro-oxidative enzyme, lipid peoxidation, γ-GT, H_2O_2 generation, blood urea nitrogen, serum creatinine, renal ODC activity and thymidine [3H] incorporation into renal DNA as a tumor promotion markers. The significant recovery of renal glutathione content, anti-oxidant enzymes and phase-II metabolising enzymes were also observed. These results indicate that soy isoflavones act as a potent chemopreventive agent against $KBrO_3$-induced renal oxidative stress, organ toxicity and subsequent cell proliferation response in female Wistar rats [64].

In the other study it was demonstrated the modulatory effects of kolaviron (200 mg/kg b.w.), a bioflavonoid from Garcinia kola seeds on the antioxidant defense mechanisms, cellular redox status and oxidative stress in the kidney and liver of male Wistar rats pretreated or treated simultaneously with $KBrO_3$ i.g. in a single dose of 300 mg/kg b.w. Kalaviron administered three times a week for 4 weeks inhibited the decrease of the activities of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) mediated by $KBrO_3$ in the kidney. Similarly, this bioflavonoid reduced the decrease in the activities of γ-GT and microsomal Ca^{2+} ATPase, and also increase in malondialdehyde (MDA) and lipid hydroperoxide formation induced by $KBrO_3$ in the kidney. Moreover, kolaviron attenuated the $KBrO_3$-decreased activities of membrane enzymes, i.e., glucose-6-phosphatase, 5'-nucleotidase and alkaline phosphatase. These data indicate the antioxidative effect of kolaviron, as a natural antioxidant. Kolaviron may therefore neutralize in the cellular redox status and depression of membrane enzyme activites caused by $KBrO_3$ in the kidney [65].

Also, extract from the red marine algae *Alsidium corallinum* exhibited cytoprotective effects against $KBrO_3$-induced erythrocyte oxidative damages in mice. *Alsidium corallinum* is widespread in the Mediterranean Sea, Madeira and the Canary Islands. One gram of algae contained 85.7 mg gallic acid (phenolic compound) and 63.4 mg quercetin (flavonoid) and richness of minerals (Ca, Mg, Na, K, Fe and small amounts of Zn, Ni, Cu, and Pb). Adult mice received $KBrO_3$ in drinking water (500 mg/L) and 7% of algae ethanolic extract via their diet for a period of 15 days. In comparison with animals which received $KBrO_3$ alone, the mice co-administered with bromate and algae extract showed a significant increase in erythrocyte (RBC), platelet, hemoglobin, and hematocrit values, and SOD and CAT activity, and also GSH and vitamin C levels in RBC. MDA and erythrocyte osmotic fragility values were reduced. In this study, the administration of A. corallinum extract had a potent protective effect against oxidative stress in RBC induced by $KBrO_3$. Moreover, have been shown the protective effects of algae extract against $KBrO_3$ genotoxicity [66].

Coumarin (1,2-benzopyrone) is a naturally occuring, heterocyclic organic compound. It is an aromatic constituent of many plants, among other *Dipteryx odorata, Asperula odorata, Cinnamonum cassia* and *Lavandum officinalus*. Coumarin is used as a fixative agent for odor in essential oils and perfumes. It is present in various soap, detergents, hair and cosmetic preparatiuons.

The structure of coumarin consists of an aromatic ring fused to a condensed lactone ring. The ring-opened products of these lactones serve as nucleophiles to scavenge the reactive, ultimate, carcinogenic metabolites. The anti-oxidative activity of phenolic compounds such as coumarin depends on the reaction of the phenol towards the chain carrying peroxyl radicals and on the stability of the phenoxyl radical formed in the reaction. Vicinal diol in phenolics chelate iron ions and transmited electrons for the redox cycle of iron ions. The anti-oxidant activity of coumarin and its derivatives is based on the coumarin nucleus. Coumarin derivatives such as 7,8-dihydroxymethylcoumarin and 7,8-diacetoxy-4-methylcoumarin have strong anti-oxidant and radical-scavenging properties [67].

Female Wistar rats were pretreated with coumarin p.o. once daily for 5 days at a dose of 10 or 20 mg/kg b.w. and than received a single i.p. injection of $KBrO_3$ at a dose of 125 mg/kg b.w. Treatment of rats with coumarin resulted in a significant decrease in γ-GT and xanthine oxidase activity, lipid peroxidation, H_2O_2 generation, BUN, serum creatinine, renal ODC activity and DNA synthesis in comparison with animals treated with $KBrO_3$ alone. Renal glutathione level and antioxidant enzyme activities, i.e., CAT, GPx, and glucose-6-phosphate dehydrogenase were also recovered to significant level. These results indicate that coumarin exerts an effective chemopreventive action against $KBrO_3$-mediated renal oxidative stress, organ toxicity and tumor promotion response in female Wistar rats [68].

Taurine (2-aminoethane sulfonic acid) is the major intracellular-free β-amino acid and is one of the few known naturally occurring

sulfonic acids. It is present in various foods like eggs, milk and is especially abundant in seafood and meat. Taurine has many essential biological roles such as conjugation of bile acids, osmoregulation, antioxidation, stabilization of membrane and modulation of calcium signaling patway. This amino acid has been shown to be essential for the development and survival of mammalian cells, especially those of the cerebellum, retina, and kidney [69].

In the study on male Wistar rats treatment with taurine at dose of 100 mg/kg b.w. for 5 days, prior to administration of $KBrO_3$ at single dose of 100 mg/kg b.w., resulted in significant attenuation in nephrotoxicity, renal lipid peroxidation and protein carbonyls, inhibition of renal BBM enzymes, and also DNA damage and DNA-protein cross-linking [70]. Similar effects were observed in the same experiment in rat intestine [71] and peripheral blood [72].

Catechol-type polyphenols are a natural or semi-synthetic products with chemoprotective activity. Oligonol is a novel biotechnology product that emanated from the oligomerization of polyphenols, typically proanthocyanidin from a variety of fruits, such as grapes, apples, and persimmons. Proanthocyanidins are naturally occurring polyphenols widely present in fruits, vegetables, barks, nuts, seeds and flowers. The extracts from the bark of pine (*Pinus maritime*) contain flavan-3-ol derivatives and have antioxidant and neuroprotective properties [73]. Grape seed extracts contain monomeric flavanols, e.g. catechin and epicatechin, oligomeric proanthocyanidins and polymeric procyanidin [74]. In the comparative study on the chemoprotective activity of above-mentioned products the order of the antioxidant activity was (-)-epigallocatechin 3-O-gallate (EGCG) > catechin > oligonol > grape seeds extracts (GSE). Oligonol significantly restored blood levels of lipid peroxidation product to the level in untreated with $KBrO_3$ rats and reduced the increased creatinine concentration in the blood. Catechin had the lowest effectiveness in normalization of the BUN and creatinine levels. Oligonol abilities to modulate $KBrO_3$-induced lipid peroxidation and the levels of BUN and creatinine suggest its chemopreventive activity and possibility of application in mitigating toxicity effects due to long-term exposure to $KBrO_3$ [75].

The compounds being an effective antioxidants, among other melatonin (N-acetyl-5-methoxytryptamine), indole-3-propionic acid, and propylothiouracyl, a thyrostatic drug, exerted protective effect against lipid peroxidation in the thyroid induced by $KBrO_3$ *in vivo* and *in vitro* [76].

Conclusion

This review presents data on some important findings concerning the toxicity and cancerogenicity of $KBrO_3$, used in both the food and cosmetics industry and being a drinking water disinfection by-product. Bromate is a strong oxidizer, and its toxicological effects are mediated via the induction of oxidative stress. Exposure to $KBrO_3$ leads to multiorgan lesions, mutagenicity, genotoxicity and carcinogenicity. These toxic effects observed in experimental animals were frequently occurred in a dose-related manner. The herbal medicines, derived from plant extracts, have been used to reduce free radical-induced tissue injury. In fact, herbal drugs and other anti-oxidants have protective effects against the toxic impact of $KBrO_3$ and other environmental contaminants due to their efficiency, the low side effects incidence, and the low cost.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Kurokawa Y, Maekawa A, Takahashi M, Hayashi Y (1990) Toxicity and carcinogenicity of potassium bromate – a new renal carcinogen. Environ Health Perspect 87: 309-335.
2. Liu Y, Mou S (2004) Determination of bromate and chlorinated haloacetic acids in bottled drinking water with chromatographic methods. Chemosphere 55: 1253-1258.
3. Fiessinger F, Rook JJ, Duguet JP (1985) Alternative methods for chlorination. Sci Total Environ 47: 299-315.
4. Gradus D, Rhoads M, Bergstrom LB, Jordan SC (1984) Acute bromate poisoning associated with renal failure and deafness presenting as hemolytic uremic syndrome. Am J Nephrol 4: 188-191.
5. Kuwahara T, Ikehara Y, Kanatsu K, Doi T, Nagai H, et al. (1984) Two cases of potassium bromate poisoning requiring long-term hemodialysis therapy for irreversible tubular damage. Nephron 37: 278-280.
6. Quick CA, Chole RA, Mauer SM (1975) Deafness and renal failure due to potassium bromate poisoning. Arch Otolaryngol 101: 494-495.
7. Warshaw BL, Carter MC, Hymes LC, Bruner BS, Rauber AP (1985) Bromate poisoning from hair permanent preparations. Pediatrics 76: 975-978.
8. Kawana K, Nakaoka T, Horiguchi Y, Watanabe S, Kawauchi S (1991) Toxicological study of potassium bromate. I. Absorption, metabolism and excretion of potassium bromate after oral administration in rats. Eisei Kaguku 37: 258-265.
9. Ahmad MK, Khan AA, Mahmood R (2012) Alterations in brush border membrane enzymes, carbo-hydrate metabolism and oxidative damage of rat intestine by potassium bromate. Biochimie 94: 2776-2782.
10. Ahmad MK, Naqshbandi A, Fareed M, Mahmood R (2012) Oral administration of a nephrotoxic dose of potassium bromate, a food additive, alters renal redox and metabolic status and inhibits brush border membrane enzymes in rats. Food Chem 134: 980-985.
11. Ahmad MK, Mahmood R (2012) Oral administration of potassium bromate, a major water disinfection by-product, induces oxidative stress and impairs the antioxidant power of rat blood. Chemosphere 87: 750-756.
12. DeAngelo AB, George MH, Kilburn SR, Moore TM, Wolf DC (1998) Carcinogenicity of potassium bromate administered in the drinking water to male B6C3F1 mice and F344/N rats. Toxicol Pathol 26: 587-594.
13. Wolf DC, Crosby LM, George MH, Kilburn SR, Moore TM, et al. (1998) Time- and dose-dependent development of potassium bromate-induced tumors in male Fischer 344 rats. Toxicol Pathol 26: 724-729.
14. Dodd DE, Layko DK, Cantell KE, Willson GA, Thomas RS (2013) Subchronic toxicity evaluation of potassium bromate in Fischer 344 rats. Environ Toxicol Pharmacol 36: 1227-1234.
15. World Health Organization (1964) Expert Committee on Food Additives. Seventh Report on the Specification for the Identity and Purity of Food Additives and Their Toxicological Evaluation: Emulsiflers, Stabilizers, Bleaching and Maturing Agents. World Health Organization Technical Report, Series 281, Geneva, p: 164.
16. Kawachi T, Yahagi T, Kada T, Tazima Y, Ishidate M, et al. (1980) Cooperative programme on short-term assays for carcinogenicity in Japan: In: Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publication No. 27, R. Montesano, H. Bartsch and L. Tomatis (eds.) International Agency for Research on Cancer, Lyon, France, pp: 330-333.
17. Ishidate M Jr, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, et al. (1984) Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22: 623-636.
18. Levin DE, Hollstein MC, Christman MF, Schwiers EA, Ames BN (1982) A new Salmonella tester strain (TA102) with A:T base pairs at the site of

mutation detects oxidative mutagens. Proc Natl Acad Sci USA 79: 7445-7449.

19. Kasai H, Nishimura S, Kurokawa Y, Hayashi Y (1987) Oral administration of the renal carcinogen, potassium bromate, specifically produces 8-hydroxydeoxyguanosine in rat target organ DNA. Carcinogenesis 8: 1959-1961.
20. Sai K, Tyson CA, Thomas DW, Dabbs JE, Hasegawa R, et al. (1994) Oxidative DNA damage induced by potassium bromate in isolated rat renal proximal tubules and renal nuclei. Cancer Lett 87: 1-7.
21. Lee YS, Choi JY, Patrk MK, Choi EM, Kasai H, et al. (1996) Induction of OH8Gua glycosylase in rat kidneys by potassium bromate (KBrO3), a renal oxidative carcinogen. Mutat Res 364: 227- 233.
22. Ballmaier D, Epe B (1995) Oxidative DNA damage induced by potassium bromate under cell-free conditions and in mammalian cells. Carcinogenesis 16: 335-342.
23. Speit G, Haupter S, Schutz P, Kreis P (1999) Comparative evaluation of the genotoxic properties of potassium bromate and potassium superoxide in V79 Chinese hamster cells. Mutat Res 439: 213-221.
24. Plewa MJ, Kargalioglu Y, Vankerk D, Minear RA, Wagner ED (2002) Mammalian cells cytotoxicity and genotoxicity analysis of drinking water disinfection by-products. Environ Mol Mutagen 40: 134-142.
25. Robbiano L, Carrozzino R, Puglia CP, Corbu C, Brambilla G (1999) Correlation between induction of DNA fragmentation and micronuclei formation in kidney cells from rats and humans and tissue-specific carcinogenic activity. Toxicol Appl Pharmaco 161: 153-159.
26. Parsons JL, Chipman JK (2000) The role of glutathione in DNA damage by potassium bromate in vitro. Mutagenesi 15: 311-316.
27. Weaver DT (1995) What to do at an end: DNA double-strand-break repair. Trends Gene 11: 388-392.
28. Harrington-Brock K, Collard DD, Chen T (2003) Bromate induces loss of heterozygosity in the Thymidine kinase gene of L5178Y/Tk+/--3.7.2C mouse lymphoma cells. Mutat Res 537: 21-28.
29. Chen T, Harrington-Brock K, Moore MM (2002) Mutant frequency and mutational spectra in the Tk and Hprt genes of N-ethyl-N-nitrosourea-treated mouse lymphoma cells. Environ Mol Muta-ge 39: 296-305.
30. Fujie K, Shimazu H, Matsuda M, Sugiyama T (1988) Acute cytogenetic effects of potassium bromate on rat bone marrow cells in vivo. Mutat Res 206: 455-458.
31. Hayashi M, Sofuni T, Ishidate M Jr (1982) High-sensitivity in micronucleus induction of a mouse strain (MS). Mutat Res 105: 253-256.
32. Awogi T, Murata K, Uejima M, Kuwahara T, Asanami S, et al. (1992) Induction of micronucleated reticulocytes by potassium bromate and potassium chromate in CD-1 male mice. Mutat Res 278: 181-185.
33. Sai K, Hayashi M, Takagi A, Hasegawa R, Sofuni T, et al. (1992) Effects of antioxidants on induction of micronuclei in rat peripheral blood reticulocytes by potassium bromate. Mutat Res 269: 113-118.
34. Suzuki T, Hayashi M, Hakura A, Asita OA, Kodama Y, et al. (1995) Combination effects of clastogens in the mouse peripheral blood micronucleus assay. Mutagenesis 10: 31-36.
35. Okada E, Fujiishi Y, Narumi K, Kado S, Wako Y, et al. (2015) Evaluation of repeated dose micronucleus assays of the liver and gastrointestinal tract using potassium bromate: a report of the collaborative study by CSGMT/JEMS.MMS. Mutat Res 780: 94-99.
36. Nakajima M, Kitazawa M, Oba K, Kitagawa Y, Toyoda Y (1989) Effect of route of administration in the micronucleus test with potassium bromate. Mutat Res 223: 399-402.
37. Kamiya H, Miura K, Ishikawa H, Inoue H, Nishimura S, et al. (1992) c-Ha-ras containing 8-hydroxyguanine at codon 12 induces point mutations at the modified and adjacent positions. Cancer Res 52: 3483-3485.
38. IARC (1999) Some Chemicals that Cause Tumors of the Kidney or Urinary Bladder in Rodents and Some Other Substances Potassium Bromate. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Lyon, pp: 481-496.
39. Kurokawa Y, Takayama S, Konishi Y, Hiasa Y, Asahina S, et al. (1986) Long-term in vivo carcinogenicity tests of potassium bromate, sodium hypochlorite, and sodium chlorite conducted in Japan. Environ Health Perspect 69: 221-235.
40. Kurokawa Y, Hayashi Y, Maekawa A, Takahashi M, Kokubo T (1982) Induction of renal cell tumors in F-344 rats by oral administration of potassium bromate, a food additive. Jpn J Cancer Res 73: 335-338.
41. Kurokawa Y, Aoki S, Matsushima Y, Takamura N, Imazawa T, et al. (1986) Dose-response studies on the carcinogenicity of potassium bromate in F344 rats after long-term oral administration. J Natl Cancer Inst 77: 977-982.
42. Kurokawa Y, Aoki S, Imazawa T, Hayashi Y, Matsushima Y, et al. (1985) Dose-related enhancing effect of potassium bromate on renal tumorigenesis in rats initiated with N-ethyl-N-hydroxyethylnitrosamine. Jpn J Cancer Res 76: 583-589.
43. Sai K, Uchiyama S, Ohno Y, Hasegawa R, Kurokawa Y (1992) Generation of active oxygen species in vitro by the interaction of potassium bromate with rat kidney cell. Carcinogenesis 13: 333-339.
44. Umemura T, Sai K, Takagi A, Hasegawa R, Kurokawa Y (1995) A possible role for oxidative stress in potassium bromate ($KBrO_3$) carcinogenesis. Carcinogenesis 16: 593-597.
45. Chung FL, Chen HJC, Nath RG (1996) Lipid peroxidation as a potential endogenous source for the formation of exocyclic DNA adducts. Carcinogenesis17: 2105-2111.
46. Marnett LJ (2000) Oxyradicals and DNA damage. Carcinogenesis 21: 361-370.
47. Sai K, Takagi A, Umemura T, Hasegawa R, Kurokawa Y (1991) Relation of 8-hydroxydeoxyguanosi-ne formation in rat kidney to lipid peroxidation, glutathione level and relative organ weight after a single administration of potassium bromate. Jpn J Cancer Res 82: 165-169.
48. Umemura T, Kitamura Y, Kanki K, Maruyama S, Okazaki K, et al. (2004) Dose-related changes of oxidative stress and cell proliferation in kidneys of male and female F344 rats exposed to potassium bromate. Cancer Sci 95: 393-398.
49. Murata M, Bansho Y, Inoue S, Ito K, Ohnishi S, et al. (2001) Requirement of glutathione and cysteine in guanine-specific oxidation of DNA by carcinogenic potassium bromate. Chem Biol Toxicol 14: 678-685.
50. Umemura T, Sai K, Takagi A, Hasegawa R, Kurokawa Y (1995) A possible role for oxidative stress in potassium bromate ($KBrO_3$) carcinogenesis. Carcinogenesis 16: 593-597.
51. Umemura T, Sai K, Takagi A, Hasegawa R, Kurokawa Y (1993) A possible role for cell proliferation in potassium bromate ($KBrO_3$) carcinogenesis. J Cancer Res Clin Oncol 119: 463-469.
52. Giri U, Iqbal M, Athar M (1999) Potassium bromate ($KBrO_3$) induces renal proliferative response and damage by elaborating oxidative stress. Cancer Lett 135: 181-188.
53. Umemura T, Tasaki M, Kijima A, Okamura T, Inoue T, et al. (2009) Possible participation of oxidative stress in causation of cell proliferation and in vivo mutagenicity in kidneys of gpt del-ta rats treated with potassium bromate. Toxicology 257: 46-52.
54. Geter DR, Ward WO, Knapp GW, Angelo AB, Rubis JA, et al. (2006) Kidney toxicogenomics of chronic potassium bromate in F344 rats. Translat Oncogenom 1: 33-52.
55. Luan Y, Suzuki T, Palanisamy R, Takashima Y, Sakamoto H, et al. (2007) Potassium bromate treatment predominantly causes large deletions, but not GC > TA transversion in human cells. Mutat Res 619: 113-123.
56. Crosby LM, Hyder KS, DeAngelo AB, Kepler TB, Gaskill B, et al. (2000) Morphologic analysis correlates with gene expression changes in cultured F344 rat mesothelial cells. Toxicol Appl Pharmacol 169: 205-221.
57. Fujii M, Oikawa K, Saito H, Fukuhara C, Onosaka S (1984) Metabolism of potassium bromate in rats. I. In vivo studies. Chemosphere 13: 1207-1212.
58. Delker D, Hatch G, Allen J, Crissman B, George M, et al. (2006) Molecular biomarkers of oxidative stress associated with bromate carcinogenicity. Toxicology 221: 158-165.

59. Tanaka K, Oikawa K, Fukuhara C, Saito H, Onosaka S, et al. (1984) Metabolism of potassium bromate in rats. II. In vitro studies. Chemosphere 13: 1213-1219.

60. Kawanishi S, Murata M (2006) Mechanism of DNA damage induced by bromate differs from general types of oxidative stress. Toxicology 221: 172-178.

61. Khan N, Sharma S, Sultana S (2003) Nigella sativa (black cumin) ameliorates potassium bromate-induced early events of carcinogenesis: diminution of oxidative stress. Hum Exp Toxicol 22: 193-203.

62. Chang LC, Gerhauser BC, Sang L, Farnsworth NR, Pezzuto JM, et al. (1997) Activity-guided isolation of constituents of T. purpurea with the potential to induce the phase II enzyme, quinone reductase. J Nat Prod 60: 869-873.

63. Khan N, Sharma S, Alam A, Saleem M, Sultana S (2001) Tephrosia purpurea ameliorates N-diethyl-nitrosamine and potassium bromate-mediated renal oxidative stress and toxicity in Wistar rats. Pharmacol Toxicol 88: 294-299.

64. Khan N, Sultana S (2004) Abrogation of potassium bromate-induced renal oxidative stress and sub-sequent cell proliferation response by soy isoflavones in Wistar rats. Toxicology 201: 173-184.

65. Farombi EO, Alabi MC, Akuru TO (2002) Kolaviron modulates cellular redox status and impairment of membrane protein activities induced by potassium bromate ($KBrO_3$) in rats. Pharmacol Res 45: 63-68.

66. Saad HB, Nasri I, Elwej A, Krayem N, Jarraya R, et al. (2014) A mineral and antioxidant- rich extract from the red marine algae Alsidium corallinum exhibits cytoprotective effects against potassium bromate-induced erythrocyte oxidative damage in mice. Biol Trace Elem Res 160: 85-96.

67. Egan DA, Kennedy R, Moran E, Thornes RD (1990) The pharmacology, metabolism, analysis and applications of coumarin and coumarin related compounds. Drug Metab Rev 22: 503-529.

68. Khan N, Sharma S, Sultana S (2004) Attenuation of potassium bromate-induced nephrotoxicity by coumarin (1,2-benzopyrone) in Wistar rats: chemoprevention against free radical-mediated renal oxidative stress and tumor promotion response. Redox Rep 9: 19-28.

69. Huxtable RJ (1992) Physiological actions of taurine. Physiol Rev 72: 101-163.

70. Ahmad MK, Khan AA, Mahmood R (2013) Taurine ameliorates potassium bromate-induced kidney damage in rats. Amino Acids 45: 1109-1121.

71. Ahmad MK, Khan AA, All SN, Mahmood R (2015) Chemoprotective effect of taurine on potassium bromate-induced DNA damage, DNA-protein cross-linking and oxidative stress in rat intestine. PLOS One 10: 1-16.

72. Ahmad MK, Mahmood R (2014) Protective effect of taurine against potassium bromate-induced hemoglobin oxidation, oxidative stress, and impairment of antioxidant defense system in blood. Environ Toxicol 29: 1-10.

73. Packer L, Rimbach G, Virgili F (1999) Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (Pinus maritime) bark. Pycnogenol. Free Rad Biol Med 27: 704-724.

74. Yilmaz Y, Toledo RT (2004) Health aspects of functional grape seed constituents. Food Sci Technol 15: 422-433.

75. Nishioka H, Fujii H, Sun B, Aruoma OI (2006) Comparative efficacy of oligonol, catechin and (-)-epigallocatechin 3-O-gallate in modulating the potassium bromate-induced renal toxicity in rats. Toxicology 226: 181-187.

76. Karbownik M, Stasiak M, Zasada K, Zygmunt A, Lewinski A (2005) Comparison of potential protective effects of melatonin, indole-3-propionic acid, and propylthiouracyl against lipid peroxydation caused by potassium bromate in the thyroid gland. J Cell Biochem 95: 131-138.