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Research Paper

Effects of Tannic Acid and Daily Intraperitoneal Beryllium Injections on Adult Male Albino Rats: Distribution and Physiological Hazards in Body Organs

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ABSTRACT

Background: Beryllium (Be) is an element used in various industries, such as nuclear and microelectronic industries. Be release into the environment raises its toxic effects and increases the likelihood of exposure to humans, which causes many hazardous side effects, such as cancer and skin allergic conditions.

Methods: This study investigated the role of tannic acid (TA) in counteracting the hazardous effects and the accumulation of Be. We made daily injections intraperitoneally into 72 adult male albino rats for 14 days. Animals were divided into four groups: control, Be, TA, and Be+TA. The animals were sacrificed at 1, 7, or 14 days into the study.

Results: The data provided evidence that Be accumulations were found in different body organs, which were ranked as follows: lung>liver>kidneys>brain>testes. Be accumulations lowered the rats' blood glucose levels significantly. In addition, the liver function tests showed significant increases in bilirubin and transaminase enzymes in the animals. We also found significant declines in alkaline phosphatase, albumin, and proteins in these animals. Further, significant rises occurred in the kidneys' secretions of creatinine, urea, uric acid, lipids, cholesterol, and triglycerides. The TA administration ameliorated the toxic effects of Be on all of the tested variables. The rise in malondialdehyde and the decline in glutathione levels in the kidneys and liver improved after the TA treatment.

Conclusion: The findings of this study provided evidence that TA administration effectively counteracted the toxic effects of Be administration in rats.

Keywords: Antioxidants, Beryllium, Kidneys, Liver, Physiological hazards, Tannic acid

Introduction

Beryllium (Be) is a light-weight metal element naturally found in the earth's crust at 2-15 mg/kg of soil. Regarding its high reactivity, it is worth mentioning that there are about 45 mineralized forms of Be, but only two of them are common as silicate minerals: beryl and bertrandite [1]. Be, whether in its elemental form or as oxide, hydroxide, and carbonate salts, is only slightly soluble or insoluble in water at a neutral pH [2]. The unique properties of Be make it suitable for many industrial uses, including inertial guidance components and microelectronics [3-5].

Based on the natural weathering of rocks, Be contamination is released variably into the environment and soil [6, 7]. Be contamination and exposure place living organisms, particularly humans, at risk of toxicity worldwide [8, 9]. More specifically, Be enters the human body via respiratory, gastrointestinal, and dermal routes. Furthermore, workers in Be mines face occupational exposure to high concentrations of soluble Be compounds, resulting in acute diseases [10, 11].

Literature Review: El-Beshbishy *et al.* [12] have shown that the administration of crocin, a major acetaminophen-based pain medicine, can reduce the oxidation of proteins and cellular lipids in adult male rats due to Be chloride. Another study [13] revealed alterations in hematological markers in female albino rates exposed to Be. This study showed that naringenin, a flavonoid antioxidant, might be useful in the natural chelating of Be. Earlier, Gordon and Bowser [14] suggested that Be was a group-1 carcinogen, based on its ability to inhibit nuclear proteins. Upon dermal exposure in rats, Be particles have caused immune sensitization effects [15]. Therefore, it is crucial to find ways to reduce the hazardous effects of Be exposure to plants, animals, and humans. In this context, numerous natural compounds extracted from plants, spices, and fruits serve as antioxidants and can inhibit free radicals released from many sources. Several studies have shown that *Saussurea lappa* root extract and alginate treatment

can inhibit the hazardous effects of thorium in adult male rats [16-18]. Cardamom extract is also known to mitigate the toxic effect of uranium on rats' brains [19-21].

Tannic acid (TA) is a large polyphenol molecule that occurs naturally and is found in numerous plants and herbs, especially tea [22]. This acid is composed of a central glucose molecule at its hydroxyl group and one or more galloyl residues. It is commonly used as a food additive, with a wide and safe dosage ranging from 10 to 400 g [23-25]. The antioxidant function of TA is due to its polyphenols, which have a hydrophobic core and a hydrophilic shell [26-28]. TA has antioxidant, anti-cancer, neuroprotective, and anti-inflammatory properties [29-33].

Aim of the Study: The current study aimed to investigate the distribution and accumulation of Be in various body organs in adult male albino rats. This study also evaluated the physiological hazards of Be on the liver and kidneys of these animals. Finally, this study investigated the antioxidant activity of TA against Be and its hazards in animals.

Materials and Methods

Chemicals: Be chloride was purchased from American Elements (Los Angeles, CA, USA). TA, EDTA, sodium acetate trihydrate, glacial acetic acid, and Chromeazurol S dye were purchased from Sigma-Aldrich (Schnelldorf, Germany). Be and TA solutions were prepared by dissolving them separately in water.

Animal Grouping: A total of 72 adult male albino rats weighing 110±20 g each were purchased from VACSERA, the holding company for biological products and vaccines (Helwan, Cairo, Egypt). The rats were housed in plastic cages (six rats/cage) at ambient laboratory conditions at 25°C under 12-hour light/dark cycles and with free access to standard rat food and water *ad libitum*. The rats were divided into four groups of 18 and treated for 14 days as follows:

1. **Control Group:** They were injected intraperitoneally (IP) with saline.
2. **Be Group:** They were injected IP with Be at 1 mg/kg of body weight.
3. **TA Group:** They were treated with 5% TA dissolved in drinking water.
4. **Be+TA Group:** They were injected IP with Be and concurrently treated with TA.

Sampling: After the 1st, 7th, and 14th days of the treatment, rats from the four groups were sacrificed (six rats each time/group). The rats' different organs (liver, kidneys, lung, brain, and testes) were separated by plastic sheets, kept in aluminum foil, and then stored in a freezer at -40°C for further analyses. During decapitation, blood samples were collected in sterile tubes, kept in a water bath at 37°C, and centrifuged for 15 min at 5000 rpm.

Tissue Digestion: A mixture of HNO_3, H_2O_2, and $HClO_4$ was placed in a Teflon beaker with each weighted organ sample. Each beaker was heated on a hot plate until it reached complete dryness. After cooling, diluted hydrochloric acid was added to the sample, and the beaker was heated again for 10 min. The volume of the samples was brought up to 25 ml with deionized water [34, 35].

Beryllium Ions Determination: Be was determined in the digested samples according to the method of Fouad *et al*. [36] using Chromeazurol S dye.

Serum Analyses: All parameters were analyzed in stored serum samples using an automated blood analyzer, the Boehringer Mannheim/Hitachi 902 system (Roche Diagnostic, Japan). The glucose contents were analyzed colorimetrically based on the method developed by Asatoor and King [37]. Transaminases and liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were quantified using the method described by Bais and Philcox [38]. Alkaline phosphatase (ALP) was measured photometrically according to Crofton's method [39]. The color intensity of the blue-green albumin is directly proportional to its concentration [40]. Albumin was determined photometrically, whereas total protein was quantified based on Simonian's method [41]. Creatinine, urea, and uric acid, which represent kidney functions, were determined according to the methods established previously [42, 43]. The cholesterol and triglyceride levels were determined by the colorimetric method described earlier [44].

Tissue Homogenization: The rats' liver and kidneys were weighted individually, homogenized in 1.2% ice-cold isotonic potassium chloride solution, and centrifuged at 5000 rpm for 10 min to separate the supernatants for the determination of malondialdehyde (MDA) and glutathione (GSH) contents.

Malondialdehyde Level: The tissue samples' MDA concentrations and the lipid peroxidation end-product were determined as thiobarbituric acid reactive substances (TBARS) according to a previously established method [45].

Glutathione Level: The reduced GSH content in each sample was determined using trichloroacetic acid and Elman's reagent [46].

Statistical Analyses: The statistical analyses of the data were expressed as mean±standard error, where the level of significance between each pair of treatments was set at $P<0.05$. Duncan's multiple-range tests and one-way analysis of variance (ANOVA) were performed using SPSS software (version 20).

Results

The daily administration of Be led to the progressive accumulation of Be ions in different body organs of the rats in the Be group in this order: lung>liver>kidneys>brain>testes, compared to the rats in the control group whose Be levels were below the detection limits (Figure 1). On the other hand, a

significant decline was found in the accumulated Be ions in the rats' different body organs after the concurrent administration of TA and Be, compared to the administration of Be alone.

The blood glucose level declined progressively following the administration of Be after 7 and 14 days into the study in the Be group, compared to the control group. In the TA group, insignificant changes in blood glucose levels were observed throughout the experiment, whereas in the Be+TA group, blood glucose levels increased compared to those of the Be group (Figure 2). The rats' total bilirubin level experienced a sudden and significant rise after the first day of Be administration and continued to rise after 7 and 14 days into the study in the Be group, compared to the control group. In the Be group, the TA administration caused a significant increase in total bilirubin level, compared to the control and Be groups. However, the daily IP injection of Be showed general disturbances in the animals' liver enzyme levels (Table 1).

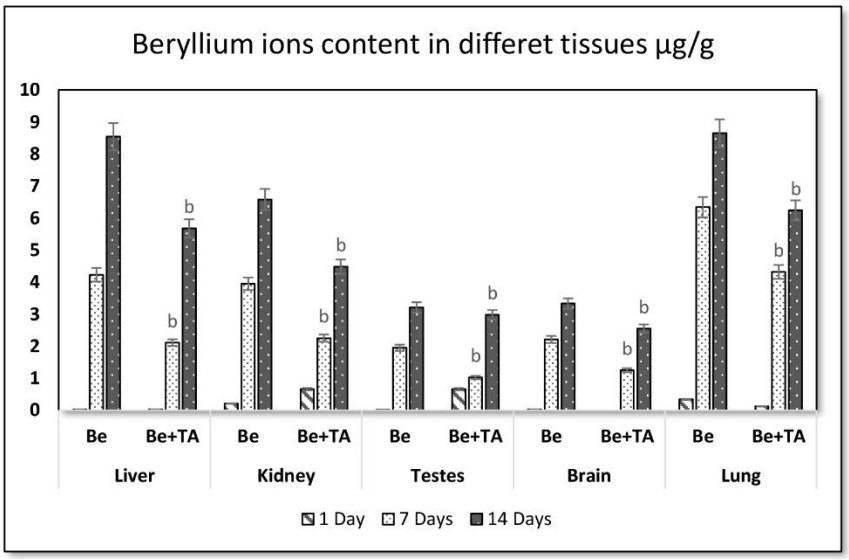

Figure 1. Effect of TA treatment on Be accumulation level (ppm) and distribution in different body organs at different time intervals. (n=6, with a significant change at P<0.05). a=control, b=Be.

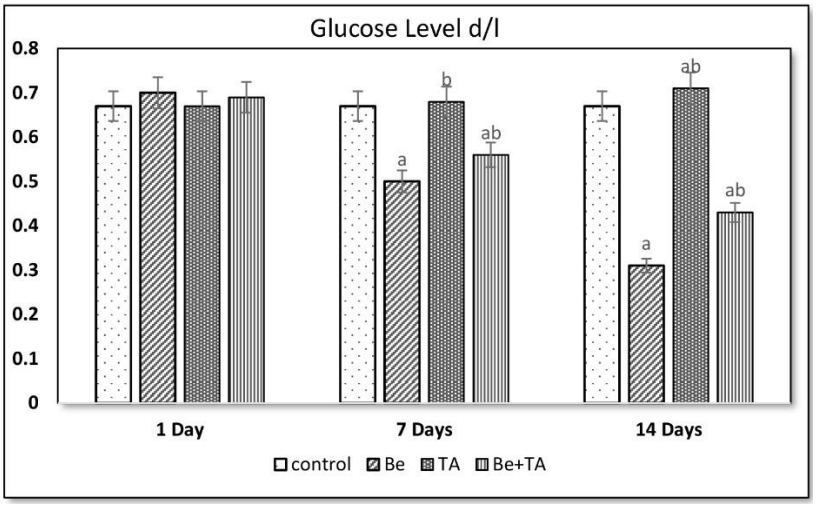

Figure 2. Effect of TA administration on blood glucose level in adult male albino rats treated with Be at different time intervals (n=6, significant change at P<0.05). a=control, b=Be.

Table 1. Effect of TA administration on different liver function tests of adult male albino rats treated with Be at different time intervals (n=6, significant change (P<0.05). a=control, and b=Be.

Day		T. Bili.	AST	ALT	Albumin	T.P.	Alk. Ph.
1 Day	Control	0.21±0.01	17.53±1.21	9.21±1.20	5.61±0.35	1.67±0.01	100.54±5.21
	Be	0.51±0.01^{a}	18.24±1.02^{a}	11.11±1.02^{a}	5.35±0.33	1.55±0.06	100.99±4.32
	TA	0.22±0.01	16.98±1.32^{a}	9.11±1.30	5.68±0.25	1.70±0.12	100.21±3.95
	Be+TA	0.32±0.03^{a}	17.55±1.01	10.21±0.98^{a}	5.55±0.66	1.5±0.09	99.25±4.26
7 Days	Be	2.55±0.10^{a}	37.66±1.95^{a}	23.12±1.32^{a}	3.11±0.47^{a}	1.02±0.08^{a}	80.33±6.59^{a}
	TA	0.19±0.02^{b}	16.32±1.01^{b}	9.22±0.89^{b}	5.89±0.65^{b}	1.89±0.12^{ab}	98.24±4.25^{ab}
	Be+TA	1.86±0.10^{ab}	32.21±2.01^{ab}	20.12±1.78^{ab}	3.95±0.65^{ab}	1.56±0.09^{b}	89.25±4.38^{ab}
14 Days	Be	2.95±0.09^{a}	58.15±2.68^{a}	36.55±2.09^{a}	2.11±0.21^{a}	0.54±0.03^{a}	68.35±6.58^{a}
	TA	0.19±0.00^{b}	15.21±1.89^{b}	8.24±0.24^{ab}	6.11±0.35^{ab}	2.11±0.12^{ab}	99.21±2.89^{b}
	Be+TA	2.01±0.10^{ab}	45.36±3.11^{ab}	30.25±2.01^{ab}	3.01±0.33^{ab}	0.78±0.18^{ab}	78.21±7.95^{ab}

In the Be group, AST and ALT enzyme levels showed a significant rise after the 1st, 7th, and 14th days of injection, compared to the control group. The ALP level began a significant decline after the 7th day of experiments and continued to decline until the 14th day. The blood AST level significantly decreased following the daily administration of TA on the first day, compared to its level in the control group. The administration of TA, along with Be, caused a significant increase in AST and ALT levels in the Be+TA group, compared to the control group. However, it showed a significant decline compared to the Be group. The blood albumin and total protein showed a significant increase after 7 and 14 days of treating the animals with TA. Both blood albumin and total protein levels in the Be and Be+TA groups showed significant declines, compared to the control group.

The IP injection of Be affected kidney function, as shown by a significant elevation in creatinine, urea, and uric acid after only one day of treatment, which continued to rise to the end of the study. On the other hand, the TA treatment, either independently or combined with Be, improved the kidney function in the TA and Be+TA group, compared to the control or the Be group (see Tables 2 and 3).

The blood MDA level showed a significant increase starting after seven days and kept increasing until the end of the study. Conversely, the reduced GSH level showed a significant decrease, compared to the control level (Figure 3). The MDA and GSH levels in the kidneys showed an inverse and proportional relationship with each other. There was a significant increase in MDA and a significant decline in the blood GSH level throughout the time when Be was being administered (Figure 4). The TA administration, alone or combined with Be, caused improvements in the blood MDA and GSH levels.

Table 2. Effect of TA administration on different kidney function tests of adult male albino rats treated with Be at different time intervals (n=6, significant change at P<0.05). a=control, b=Be.

	Parameters	Create.	Urea	Uric acid
1 Day	control	0.50±0.01	2.12±0.14	0.14±0.01
	Be	0.68±0.02[a]	1.91±0.11[a]	0.19±0.01[a]
	TA	0.51±0.01	2.00±0.09	0.07±0.00[a]
	Be+TA	0.51±0.02	2.14±0.10	0.15±0.00
7 Days	Be	0.89±0.02[a]	3.55±0.12[a]	0.24±0.01[a]
	TA	0.51±.0.01[b]	2.05±0.13[b]	0.02±0.00[ab]
	Be+TA	0.76±0.02[ab]	2.68±0.21[ab]	0.18±0.0[ab]
14 Days	Be	1.21±0.12[a]	4.02±0.21[a]	0.58±0.01[a]
	TA	0.45±0.01[b]	2.15±0.19[b]	0.03±0.00[ab]
	Be+TA	0.89±0.02[ab]	3.56±0.28[ab]	0.29±0.01[ab]

Table 3. Effect of TA administration on cholesterol and triglyceride levels in adult male albino rats treated with Be at different time intervals (n=6, significant change at P<0.05). a=control, b=Be.

Day	Parameters	Cholesterol	Triglyceride
1 Day	Control	30.25±2.10	28.55±1.24
	Be	32.21±2.35[a]	29.32±1.55[a]
	TA	30.22±2.47	28.56±1.12
7 Days	Be+TA	30.55±3.25	28.99±2.01
	Be	36.58±3.22[a]	32.59±1.35[a]
	TA	29.56±2.68	27.95±1.55[a]
14 Days	Be+TA	34.56±1.25[ab]	30.25±1.24[ab]
	Be	42.32±3.25[a]	35.66±1.65[a]
	TA	28.54±2.54[a]	25.36±.68[a]
	Be+TA	40.22±3.44[ab]	32.89±0.99[ab]

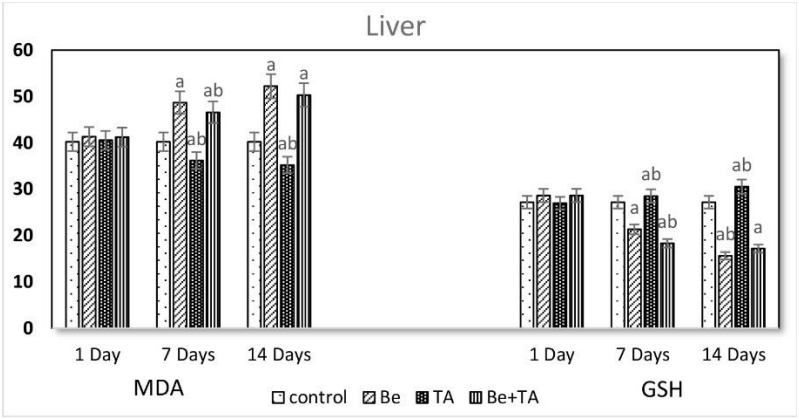

Figure 3. Effect of TA administration on liver MDA and GSH in adult male albino rats treated with Be at different time intervals (n=6, significant changes at P<0.05). a=control, b=Be.

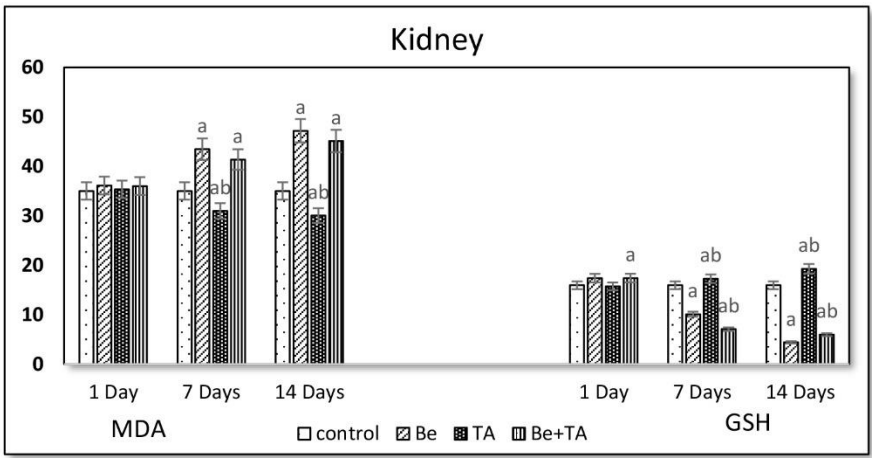

Figure 4. Effect of TA administration on kidney MDA and GSH levels in adult male albino rats treated with Be at different time intervals (n=6, significant changes at P<0.05). a=control, b=Be.

Discussion

Generally, most soluble Be salts in water are hydrolysable to Be hydroxide at neutral pH levels, leaving only trace amounts of dissolved Be ions. At high pH levels, however, water-soluble hydroxide complexes may form, enhancing the Be's solubility and mobility. Within the physiological range (pH 5-8), Be tends to form hydroxides or hydrated complexes [47]. Therefore, the formation of different Be species in the body organs depends on the medium pH being cationic in acidic environments, such as the stomach. At neutral or alkaline pH levels, as in the blood and intestine, Be becomes anionic. Further, the surface of TA is positively charged at low pH (e.g., pH≤3) due to the protonation effect. At higher pH levels, this effect declines, and TA surface becomes negatively charged due to the ionization of its OH groups. Therefore, the positively charged Be species may bind to and be adsorbed on the TA surface by electrostatic interaction, as shown in Figure 5 [47]. The adsorptive affinity of TA toward Be ions may be the reason for TA to counteract the effect of Be on the rats. The adsorption of Be species to TA decreases its concentration in biological fluids, thereby lowering its accumulation and hazardous effects.

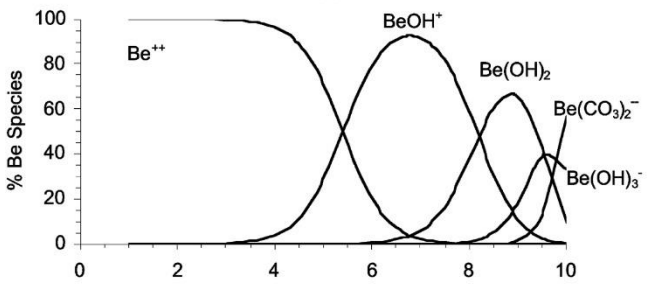

Figure 5. Beryllium speciation at varying pH levels.

Be is transported via the bloodstream and is readily distributed in various animal organs [48]. The present study has shown the ability of Be to distribute differently and accumulate in various body organs, which is consistent with the findings of previous studies [49, 50]. The reason for the higher levels of Be in the lungs relative to other body organs may be that soluble Be salts are converted to less soluble forms in the lung. On the other hand, the combined TA and Be treatment showed the capacity of TA to decrease the Be accumulation in the organs. Our results suggest that TA effectively adsorbs Be compounds, which is consistent with the reports of previous studies for its similar effects against Cu, Cd, Fe, Zn, and Mn [51, 52]. The blood glucose level is considered an indication of its metabolism in the body and liver. Our findings demonstrated a significant fall in the blood glucose level, which may reflect hypoglycemia due to liver damage.

Our results are also in agreement with Nirala and Bhadauria [53], demonstrating that exposure to toxic metals, such as Be, inactivates hexokinase, phosphoglucomutase, and other enzymes with major roles in carbohydrate metabolism. The impaired metabolism may also be due to a decline in the hepatic glycogen storage that occurs after liver damage [54]. An earlier study [55] has suggested that TA administration in animals modulates the enzymatic activities of phases I and II in the tissues. Further, Crespy and Williamson [56] have shown that TA catechins are the phenolic compounds that activate the insulin signaling pathway as they regulate glucose transport and lead to the reduction or prevention of type 2 diabetes [57]. These findings may support the reason why TA had an improving effect on the rats' blood glucose levels in the present study. Catechins are substances found in tea that help protect cells against free radicals and are known to inhibit cancer, tumor growth and angiogenesis, and cell invasion.

It is known that, when red blood cells outlive their life and become too fragile in circulation, the broken heme rings release their iron and pyrrole nuclei to form biliverdin. This event leads to the generation of bilirubin via the conjugation process in the liver, demonstrating the reasons for the increase in bilirubin levels in the

blood. It has been shown that Be administration causes severe hemolysis and significant reductions in hemoglobin concentration and red blood cell count [58]. This finding may explain the highly significant increase in bilirubin in the present study, which is evident in the general features of the studied animals, such as the ball-yellow color of the rat's ears (Figure 6). In this context, an earlier study [59] has also shown that TA inhibits hemorrhage due to its polyphenol components, thereby protecting the animals from dying [60].

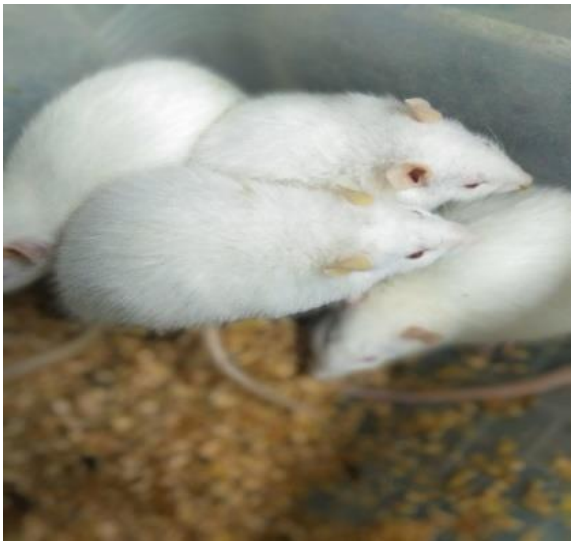

Figure 6. The ball-yellow color of the rats' ears

Metal intoxication is responsible for oxidative stress and leads to depletion of reduced GSH [61]. Another study has also reported the depletion of GSH due to Be administration [62]. In the present study, there was a decline in the liver and kidney GSH levels resulting from the Be administration. We believe that this event might have occurred due to the binding of Be to the active sites of the involved enzymes. The dietary polyphenols in TA are likely to scavenge free radicals with their highly effective electron donors. Other studies have suggested that TA has high antioxidant effects *in vitro*, compared to gallic and caffeic acids [50, 63]. TA also enhances the antioxidant ability of superoxide dismutase [56]. Therefore, the evidence supports the findings of the present study with respect to the effect of TA on the GSH levels in the rats.

Further, we found a significant rise in MDA levels after Be administration. This finding suggests that cytochrome P-450 might have been inhibited due to the hydroxylation of the substrates, secondary to the generation of reactive oxygen species as a result of Be toxicity [64]. On the other hand, TA, with its potential antioxidant effects, might have scavenged free radicals, thereby inhibiting lipid peroxidation. Two studies have shown that the intravenous administration of TA has caused hypotension in normotensive rats and lowered the blood triglycerides and MDA levels [65, 66].

Be treatment can elevate cholesterol and triglycerides sharply, causing alternations in lipid profiles and metabolic disturbances in liver function. The current study demonstrated elevations in liver transaminases (AST and ALT), together with depletions in ALP, albumin, and total proteins. This evidence establishes the disturbance in the liver metabolic function arising from Be intoxication. The metabolic alteration after the Be treatment is highly likely due to severe histopathological and necrotic damage to the liver. It is also indicative of the ability of Be to displace magnesium ions secondary to the depletion of ALP [61]. The findings of the current study are consistent with those of Mathur and Flora [67], demonstrating that Be caused significant rises in animals' liver enzymes. Support for our findings also comes from Witschi and Aldridge's study [68], showing a significant decrease in ALP and albumin levels after Be treatment in an animal model. The depletion in total protein and albumin in the present study may be due to the ability of Be to inhibit nuclear protein synthesis in addition to its damaging effects on DNA transcription and gene expression [69].

It is well known that kidneys excrete toxic substances and ions from the blood into the urine while returning useful molecules and substances back to the blood [58]. Therefore, Be residues that enter body organs move into the bloodstream and are excreted by the kidneys into the urine. Other indirect effects of Be administration are believed to be weight loss, kidney stone formation, and hepatic necrosis [40]. The current study found evidence of kidney dysfunction after Be administration, which was consistent with the results of former research by Ward and Okun [70], reporting renal failure, sclerosis, and nephritis in workers employed at Be manufacturing facilities. Another study [53] has also demonstrated renal ultrastructural disturbances, that is, cytoplasmic condensation, loosely arranged mitochondria, and vacuolation [71]. Additionally, significant rises have been reported by two earlier studies [53, 67] in the levels of ALP, acid phosphatase, and lipid peroxidation, as well as a reduction in the kidneys' glycogen levels. The polyphenolic compounds of TA can scavenge free radicals by inhibiting the MDA level in the kidneys. Lastly, two recent studies [72, 73] have reported significant improvements in the blood pressure of hypertensive rats after they were treated with TA.

Conclusions

The hazardous effects of Be may be due in part to the entrance of Be into different body organs, causing lesions or damage to organ tissues. It may be due to the overstimulation effect of MDA, which results from the rise in the reactive oxygen species leading to GSH depletion over time. The IP injection of Be induced hepatic hazardous effects, such as significant increases in bilirubin and transaminase enzymes, and a major decrease in ALP, albumin, and protein production levels.

The daily administration of 5% TA showed that it played a role in the mitigation of the damages caused by Be. This effect may be associated with the adsorption and antioxidant properties of TA. Finally, TA administration ameliorated the hazardous effects of Be toxicity.

Conflict of Interests

The authors declare no conflict of interests with any entities.

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Compliance with Ethical Guidelines

The study protocol was approved by the Ethics Committee of the Nuclear Material Authority, which is conducted in accordance with the ethical standards laid down by the US guidelines (NIH Publication No. 85-23, amended in 1985).

Authors' Contributions

M.M.R. and M.O.A.E.M. conceived the study's initial idea. M.M.R., W.M.M., W.S.H., S.H.N., and M.O.A.E.M. verified the analytical methods and carried out the experiments with support from T.F.M. and M.F.C. M.M.R. and M.O.A.E.M. wrote the manuscript with input from all authors. All authors provided critical review of the study protocol and helped in shaping the research design, data analyses, and drafting the initial manuscript. All authors carefully reviewed the text and contributed to the final draft of the manuscript.

References

1. Ayuso RA, Foley NK. Metallogeny and exploration strategy for volcanic rocks hosting world class Be-UF mineralization at Spor Mountain, Utah, USA. J Geochem Explor. 2023;**247**:107154. [**doi**:10.1016/j.gexplo.2023.107154]
2. Bolan S, Wijesekara H, Tanveer M, Boschi V, Padhye LP, Wijesooriya M, et al. Beryllium contamination and its risk management in terrestrial and aquatic environmental settings. Environmental Pollution. 2023;**320**:121077. [**doi**:10.1016/j.envpol.2023.121077]
3. ZhongS, HuM, Zhang L, QinX, ZhangQ, RuX, WangL.Toxic metals and the risks of sludge from the treatment of wastewater from beryllium smelting. Chemosphere. 2023;**326**:138439. [**doi**:10.1016/j.chemosphere.2023.138439]
4. Martin-Somer A, Lamsabhi AM, Mo O, Yanez M. The importance of deformation on the strength of beryllium bonds. Computational and Theoretical Chemistry. 2012;**998**:74-9. [**doi**:10.1016/j.comptc.2012.06.009]
5. Zuanetti B, Ramos K, Cady C, Golder A, Meredith C, Casem D, Bolme C, editors. High strain-rate testing of brittle materials using miniature beryllium split-hopkinson pressure bars. In: Zhang, M., et al. Characterization of Minerals, Metals, and Materials. The Minerals, Metals & Materials Series. 2023:65-73. [**doi**: 10.1007/978-3-031-22576-5-7]
6. DHHS U, Health UDo, Services H. Hazardous substances data bank (HSDB, online database). National Toxicology Information Program, National Library of Medicine, Bethesda, MD. 1993. [Link]
7. Suhrhoff TJ, Rickli J, Crocket K, Bura-Nakic E, Vance D. Behavior of beryllium in the weathering environment and its delivery to the ocean. Geochimica et Cosmochimica Acta. 2019;**265**:48-68. [**doi**:10.1016/j.gca.2019.08.017]
8. Castorina R, Woodruff TJ. Assessment of potential risk levels associated with US Environmental Protection Agency reference values. Environ Health Perspect. 2003;**111**(10):1318-25. [Link]
9. Kutzman RS, Gimon DM, Hinz JP, TX NSA. Identification of Chemicals of Interest to the Department of Defense and US Air Force Among the US Environmental Protection Agency's Integrated Risk Information System Chemicals that are due for Reassessment of their Toxicity Values. 2010 . [Link]
10. Renfew MM. NIOSH Pocket guide to chemical hazards (US Department of Health and Human Services-National Institute for Occupational Safety and Health). ACS Publications.1991. [Link]
11. Berger JL, Riskin SD. Economic and Technological Feasibility in Regulating Toxic Substances Under the Occupational Safety and Health Act. Ecology LQ. 1978;**7**:285. [Link]
12. El-Beshbishy HA, Hassan MH, Aly HA, Doghish AS, Alghaithy AA. Crocin "saffron" protects against beryllium chloride toxicity in rats through diminution of oxidative stress and enhancing gene expression of antioxidant enzymes. Ecotoxicol Environ Saf. 2012;**83**:47-54. [**doi**:10.1016/j.ecoenv.2012.06.003]
13. Verma A, Rakshit S, Nirala Sk, Bhadauria N. Beryllium driven hematological and serological alteration; that cured by chelation via naringenin in albino rats. Asian J Pharm Clin Res. 2019;**12**(9):116-9. [**doi**:10.22159/ajpcr.2019.v12i9.34517]
14. Gordon T, Bowser D. Beryllium: genotoxicity and carcinogenicity. Mutat Res /Fundamental & Molecular Mechanisms of Mutagenesis. 2003;**533**(1-2):99-105. [**doi**:10.1016/j.mrfmmm.2003.08.022]
15. Clayton GM, Wang Y, Crawford F, Novikov A, Wimberly BT, Kieft JS, et al. Structural basis of chronic beryllium disease: linking allergic hypersensitivity and autoimmunity. Cell. 2014;**158**(1):132-42. [**doi**:10.1016%2fj.cell.2014.04.048]
16. Rezk MM. A neuro-comparative study between single/successive thorium dose intoxication and alginate treatment. Biol Trace Element Res. 2018;**185**:414-23. [**doi**:10.1007/s12011-018-1262-9]
17. Abdel-Rahman M, Rezk MM, Abdel Moneim AE, Ahmed-Farid OA, Essam S. Thorium exerts hazardous effects on some neurotransmitters and thyroid hormones in adult male rats. Naunyn-Schmiedeberg's Arch Pharmacol. 2020;**393**:167-76. [**doi**:10.1007/s00210-019-01718-y]
18. Abdel-Rahman M, Rezk MM, Ahmed-Farid OA, Essam S, Abdel Moneim AE. *Saussurea lappa* root extract ameliorates the hazards effect of thorium induced oxidative stress and neuroendocrine alterations in adult male rats. Environ Sci Pollut Res. 2020;**27**:13237-46. [**doi**:10.1007/s11356-020-07917-y]
19. Kader SMA, Bauomi AA, Abdel-Rahman M, Mohammaden TF, Rezk MM. Antioxidant potentials of (Elletaria cardamomum) cardamom against uranium hazards. Int J Basic Life Sci. 2015;**3**(4):164-81. [Link]
20. Abdel-Rahman M, Bauomi A, Abdel-Kader S, Mohammaden T, Rezk MM. Effect of cardamom (Elletaria cardamomum) on brain ions and acetylcholine esterase enzyme of albino rats ingested uranium. Int J Basic Life Sci. 2015;**3**(3):122-38. [Link]
21. Abdel-Rahman M, Rezk MM, Kader SA. The role of cardamom on the hazardous effects of depleted uranium in cerebellum and midbrain of albino rats. Toxicol Environ Health Sci. 2017;**9**:64-73. [**doi**:10.1007/s13530-017-0305-5]
22. Chen P-Y, Liao Y-H, Huang W-T, Lin Y-C, Hou Y-T. Effects of tannic acid on liver function in a small hepatocyte–based detachable microfluidic platform. Biochem Engin Journal. 2023;**190**:108757. [**doi**:10.1016/j.bej.2022.108757]
23. Chen S-C, Chung K-T. Mutagenicity and antimutagenicity studies of tannic acid and its related compounds. Food Chem Toxicol. 2000;**38**(1):1-5. [**doi**:10.1016/S0278-6915(99)00114-3]
24. Wei C, Wang C-L, Hao Y-J, Zhang X, Long J-S, Lang W-Z. Nature-inspired construction of poly (vinylidene fluoride) membranes through the coordination coating of tannic acid with copper ions for oil-in-water emulsions separation. Journal of Membrane Science. 2023;**671**:121367. [**doi**:10.1016/j.memsci.2023.121367]
25. Isenburg JC, Karamchandani NV, Simionescu DT, Vyavahare NR. Structural requirements for stabilization of vascular elastin by polyphenolic tannins. Biomaterials. 2006;**27**(19):3645-51. [**doi**:10.1016/j.biomaterials.2006.02.016]
26. Wu L, Chu C, Chung J, Chen C-H, Hsu L-S, Liu J-K, Chen S. Effects of tannic acid and its related compounds on food mutagens or hydrogen peroxide-induced DNA strands breaks in human lymphocytes. Mutation Research - Fundamental and Molecular

Mechanisms of Mutagenesis. 2004;**556**(1-2):75-82. [**doi**:10.1016/j.mrfmmm.2004.07.004]
27. Lopes GK, Schulman HM, Hermes-Lima M. Polyphenol tannic acid inhibits hydroxyl radical formation from Fenton reaction by complexing ferrous ions. Biochimica et Biophysica Acta General Subjects. 1999;**1472**(1-2):142-52. [**doi**:10.1016/S0304-4165(99)00117-8]
28. Aguilar CN, Rodríguez R, Gutiérrez-Sánchez G, Augur C, Favela-Torres E, Prado-Barragan LA, et al. Microbial tannases: advances and perspectives. Appl Microbiol Biotechnol. 2007;**76**:47-59. [**doi**:10.1007/s00253-007-1000-2]
29. Andrade Jr RG, Dalvi LT, Silva Jr JMC, Lopes GK, Alonso A, Hermes-Lima M. The antioxidant effect of tannic acid on the in vitro copper-mediated formation of free radicals. Archives of Biochemistry and Biophysics. 2005;**437**(1):1-9. [**doi**:10.1016/j.abb.2005.02.016]
30. Bance R, Teel R. Effect of tannic acid on rat liver S9 mediated mutagenesis, metabolism and DNA binding of benzo [a] pyrene. Cancer Lett. 1989;**47**(1-2):37-44. [doi:10.1016/0304-3835(89)90174-2]
31. Khan W, Wang Z, Athar M, Bickers D, Mukhtar H. Inhibition of the skin tumorigenicity of (±)-7β, 8α-dihydroxy-9α, 10α-epoxy-7, 8, 9, 10-tetrahydrobenzo [a] pyrene by tannic acid, green tea polyphenols and quercetin in Sencar mice. Cancer Lett. 1988;**42**(1-2):7-12. [**doi**:10.1016/0304-3835(88)90232-7]
32. Mahmood H, Asif M, Khalid SH, Khan IU, Chauhdary Z, Razzaq FA, et al. Design of a multifunctional carrageenan-tannic acid wound dressing co-loaded with simvastatin and geranium oil. J Drug Delivery Sci Technol. 2023;**79**:104080. [**doi**:10.1016/j.jddst.2022.104080]
33. Cen D, Zheng Q, Zheng B, Zhou R, Xiao X, Zhang T, et al. A Near-Infrared Light-Responsive ROS Cascade Nanoplatform for Synergistic Therapy Potentiating Antitumor Immune Responses. Adv Funct Mater. 2023;**33**(9):2211402. [**doi**:10.1002/adfm.202211402]
34. FAO. Report of the Third Session of the Working Party on Pollution and Fisheries. Food Administration Organizationn'Committee for Inland Fisheries of Africa .1992. [Link]
35. Cicik B, Engin K. The effects of cadmium on levels of glucose in serum and glycogen reserves in the liver and muscle tissues of Cyprinus carpio (L., 1758). Turkish Journal of Veterinary & Animal Sciences. 2005;**29**(1):113-17. [Link]
36. Fouad HK, Atrees MS, Badawy WI. Development of spectrophotometric determination of beryllium in beryl minerals using chrome Azurol S. Arab J Chem .2016;**9**:S235-S9. [doi:10.1016/j.arabjc.2011.03.012]
37. Asatoor AM, King EJ. Simplified colorimetric blood sugar method. Biochem J. 1954;56(325th Meeting):xliv. [Link]
38. Bais R, Philcox M. Approved recommendation on IFCC methods for the measurement of catalytic concentration of enzymes. Part 8. IFCC Method for Lactate Dehydrogenase (l-Lactate: NAD+Oxidoreductase, EC 1.1.1.27). Intl Federation Clin Chem. Eur J Clin Chem Clin Biochem. 1994;**32**(8):639-55. [**pmid**: 7819436]
39. Crofton PM. Biochemistry of alkaline phosphatase isoenzymes. Crit Rev Clin Lab Sci. 1982;**16**(3):161-94. [**doi**:10.3109/10408368209107027]
40. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Lernmark Å, et al. Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus. Clin Chem. 2023;**69**(8): 808-68. [**doi**:10.1093/clinchem/hvad080]
41. Simonian MH. Spectrophotometric determination of protein concentration. Curr Protoc Cell Biol. 2002; **15**(1), A-3B. [**doi**:10.1002/0471142913.fab0103s04]
42. Larpent L, Verger C. The need for using an enzymatic colorimetric assay in creatinine determination of peritoneal dialysis solutions. Perit Dial Int. 1990;**10**(1):89-92. [**doi**:10.1177/089686089001000122]
43. Wang X, Li F, Cai Z, Liu K, Li J, Zhang B, He J. Sensitive colorimetric assay for uric acid and glucose detection based on multilayer-modified paper with smartphone as signal readout. Anal Bioanal Chem. 2018;**410**(10):2647-55. [**doi**:10.1007/s00216-018-0939-4]
44. Moghadasian MH, Frohlich JJ, Scudamore CH. Specificity of the commonly used enzymatic assay for plasma cholesterol determination. J Clin Pathol. 2002;**55**(11):859-61. [**doi**:10.1136/jcp.55.11.859] [**pmid**: 12401826]
45. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Analyt Biochem. 1979;**95**(2):351-58. [**doi**:10.1016/0003-2697(79)90738-3]
46. Ellman GL. Tissue Sulfhydryl Groups. Archives of Biochemistry and Biophysics. 2022;726:109245. [**doi**:10.1016/0003-9861(59)90090-6]
47. Sutton M, Burastero SR. Beryllium chemical speciation in elemental human biological fluids. Chem Res Toxicol. 2003;**16**(9):1145-54. [**doi**:10.1021/tx0256477]
48. Bruce R, Ingerman L, Jarabek A. Toxicological Review of Beryllium and Compounds. Environmental Protection Agency.1998. [Link]
49. Drobyshev E, Kybarskaya L, Dagaev S, Solovyev N. New insight in beryllium toxicity excluding exposure to beryllium-containing dust: accumulation patterns, target organs, and elimination. Arch Toxicol. 2019;**93**(4):859-69. [**doi**:10.1007/s00204-019-02432-7]
50. Sharma P, Shah A, Shukla S. Protective effect of Tiron (4,5-dihydroxybenzene-1,3-disulfonic acid disodium salt) against beryllium-induced maternal and fetal toxicity in rats. Arch Toxicol. 2002;**76**(8):442-48. [**doi**:10.1007/s00204-002-0356-4]
51. Üçer A, Uyanik A, Aygün ŞF. Adsorption of Cu(II), Cd(II), Zn(II), Mn(II) and Fe(III) ions by tannic acid immobilised activated carbon. Sep Purif Technol. 2006;**47**(3):113-8. [**doi**:10.1016/j.seppur.2005.06.012]
52. Ganai SA, Mir MA, Shah BA, Qadri RA, Wani AH, Rajamanikandan S, et al. Evaluation of free radical quenching, anti-inflammatory activity together with anticancer potential of *Lychnis coronaria* and characterization of novel molecules from its extract through high resolution-liquid chromatography mass spectrometry coupled to structural biochemistry approach. J Biomol Struct Dyn. 2023:**41**(22) 13041-055. [**doi**:10.1080/07391102.2023.2173296]
53. Nirala SK, Bhadauria M, Shukla S, Agrawal OP, Mathur A, Li PQ, et al. Pharmacological intervention of tiferron and propolis to alleviate beryllium-induced hepatorenal toxicity. Fundam Clin Pharmacol. 2008;**22**(4):403-15. [doi:10.1111/j.1472-8206.2008.00603.x]
54. Teixeira CFP, Yasaka WJ, Silva LF, Oshiro TT, Oga S. Inhibitory effects of beryllium chloride on rat liver microsomal enzymes. Toxicology. 1990;**61**(3):293-301. [**doi**:10.1016/0300-483X(90)90179-K.
55. Krajka-Kuźniak V, Baer-Dubowska W. The effects of tannic acid on cytochrome P450 and phase II enzymes in mouse liver and kidney.Toxicol Lett. 2003;**143**(2):209-16. [**doi**:10.1016/S0378-4274(03)00177-2]
56. Crespy V, Williamson G. A review of the health effects of green tea catechins in in vivo animal models. J Nutrition. 2004;**134**(12):3431S-40S. [**doi**:10.1093/jn/134.12.3431S]
57. Hiller J, Naglav-Hansen D, Drexler H, Göen T. Human urinary and blood toxicokinetics of beryllium after accidental exposure. J Trace Elem Med Biol. 2023;**76**:127125. [**doi**:10.1016/j.jtemb.2023.127125]
58. Hall JE and HallME. Guyton and Hall textbook of medical physiology e-Book. 2020: Elsevier Health Sciences. [Link]
59. Kuppusamy UR, Das NP. Protective effects of tannic acid and related natural compounds on Crotalus adamenteus subcutaneous poisoning in mice. Pharmacol Toxicol.1993;**72**(4-5):290-95. [**doi**:10.1111/j.1600-0773.1993.tb01652.x]
60. Sekizawa J. Concise International Chemical Assessment Document (CICAD): a new chemical safety series in IPCS, internationalizing national reviews. Eisei Shikenjo Hokoku. 1996;**114**:89-94. [**pmid**: 9037872]
61. Nirala SK, Bhadauria M, Mathur R, Mathur A. Amelioration of beryllium induced alterations in hepatorenal biochemistry and ultramorphology by co-administration of tiferron and adjuvants. J Biomed Sci.2007;**14**(3):331-45. [**doi**:10.1007/s11373-007-9147-5]
62. Faraci WS, Zorn SH, Bakker AV, Jackson E, Pratt K. Beryllium competitively inhibits brain *myo-inositol* monophosphatase, but unlike lithium does not enhance agonist-induced inositol phosphate accumulation. Biochem J.1993;**291**(2):369-74. [**doi**:10.1042/bj2910369]
63. Pulido R, Bravo L, Saura-Calixto F. Antioxidant activity of dietary polyphenols as determined by a modified ferric reducing/antioxidant power assay. J Agric Food Chem. 2000;**48**(8):3396-402. [**doi**:10.1021/jf9913458]
64. Bodrenko I, Satta A, Caddeo C, Cozzolino G, Milenkovic S, Ceccarelli M, et al. Promising perspectives on the use of fullerenes as efficient containers for beryllium atoms. Adv Funct Mater. 2023;**33**(42):2303786. [**doi**:10.1002/adfm.202303786]
65. Yugarani T, Tan BK, Das NP. The effects of tannic acid on serum lipid parameters and tissue lipid peroxides in the spontaneously hypertensive and Wistar Kyoto rats. Planta Med. 1993;**59**(1):28-

31. [**doi**:10.1055/s-2006-959598]
66. Fukuda N, Yoshitama A, Sugita S, Fujita M, Murakami S. Dietary taurine reduces hepatic secretion of cholesteryl ester and enhances fatty acid oxidation in rats fed a high-cholesterol diet. J Nutr Sci Vitaminol (Tokyo). 2011;**57**(2):144-49. [**doi**:10.3177/jnsv.57.144]
67. Mathur S, Flora SJ, Mathur R, Das Gupta S. Mobilization and distribution of beryllium over the course of chelation therapy with some polyaminocarboxylic acids in the rat. Hum Exp Toxicol. 1993;**12**(1):19-24. [**doi**:10.1177/096032719301200104]
68. Witschi HP, Aldridge WN. Uptake, distribution and binding of beryllium to organelles of the rat liver cell. Biochem J. 1968;**106**(4):811-20. [**doi**:10.1042%2Fbj1060811] [**pmid**: 5637364]
69. Parker VH, Stevens C. Binding of beryllium to nuclear acidic proteins. Chem Biol Interact. 1979;**26**(2):167-77. [**doi**:10.1016/0009-2797(79)90020-6] [**pmid**: 455565]
70. Ward E, Okun A, Ruder A, Fingerhut M, Steenland K. A mortality study of workers at seven beryllium processing plants. Am J Ind Med. 1992;22(6):885-904. [**doi**:10.1002/ajim.4700220610] [**pmid**: 1463033]
71. Kuschner M. The carcinogenicity of beryllium. Environ Health Perspect. 1981;**40**:101-5. [**doi**: 10.1289/ehp.8140101] [**pmid**: 7023926]
72. Xu J, Chen TY, Tai CH, Hsu SH. Bioactive self-healing hydrogel based on tannic acid modified gold nano-crosslinker as an injectable brain implant for treating Parkinson's disease. Biomater Res. 2023;**27**(1):8. [**doi**: 10.1186/s40824-023-00347-0] [**pmid**: 36755333]
73. Gülçin İ, Huyut Z, Elmastaş M, Aboul-Enein HY. Radical scavenging and antioxidant activity of tannic acid. Arab J Chem. 2010;**3**(1):43-53. [**doi**:10.1016/j.arabjc.2009.12.008].