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ORIGINAL ARTICLE **OPEN ACCESS**

Selenium in combination with tellurium protects the toxicity of tellurium in the liver mitochondria of rats

Mohammed M. Safhi [1] , Mohammad Firoz Alam [1*] , Gulrana Khuwaja [2] ,Mohammad Ashafaq [1] , Andleeb Khan [1] , Farah Islam [3] , Tarique Anwer [1] , Gyas Khan, S M Sivakumar [3] , Fakhrul Islam [1*]
[1] Department of Pharmacology and Toxicology, College of Pharmacy, Jazan University, K.S. A.
[2] Department of Pharmaceutical Chemistry, College of Pharmacy, Jazan University, K.S.A.
[3] Department of Pharmaceutics, College of Pharmacy, Jazan University, K.S.A
***Corresponding Author's** Email: firozalam309@gmail.com; drfislam@gmail.com

ABSTRACT
Selenium (Se) essentially required for the health at the micro level, but is toxic beyond micro concentration. There is no report of tellurium (Te) being used for the health. The humans are always exposed to various kinds of toxicants at their occupation. The workers of Se and Te manufacturer are also exposed to it and other toxicants. There is need to investigate the toxic effect of Se and Te as individually and in the combined form. Therefore, the present study focused on the combined toxicity of Se and Te in the liver mitochondria of male Wistar rats. Five groups of rats were made, control, Te-2 (4.15 mg/kg) treated, Te-1 (2.075 mg/kg) + Se-1 (0.15 mg/kg) treated, Te-2 (4.15 mg/kg) + Se-2 (0.3 mg/kg) treated and Se-2 (0.3 mg/kg) treated. Te as sodium tellurite (orally) and "Se" as sodium selenite (i.p.) was given for 15 days. On day 16, livers were dissected out for the isolation of mitochondria. The activities of caspase-3 and -9 were protected significantly with the treatment of Se-2 in Te-2+Se-2 and Se-2 groups as compared to Te-2 group. There is no report of Te on the activity of caspase-3 and -9 as well as their activation by Se. So this study describes the first report of Te and Se on the activity of caspase-3 and -9. The Te-2 group has shown a significantly increased level of lipid peroxidation (LPO)as compared to control group. On the other hand, this level was protected in Te-1 + Se-1, Te-2 + Se-2 and Se-2 groups as compared to Te-2 group. Both the doses of Se have protected its level in the groups of Te-1 + Se-1 and Te-2 + Se-2 as compared to Te-2 group. The content of GSH and the activities of GPx, GR, SOD and CAT were decreased significantly in Te-2 group as compared to control group, but these changes were protected by the addition of Se in the groups of Te-1 + Se-1 and Te-2 + Se-2 groups as compared to Te-2 group. So it is concluded that Se protects against the toxicity of Te in the liver mitochondria of rats using various biomarkers.
Key words: selenium, tellurium, liver mitochondria, oxidative stress, apoptosis

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INTRODUCTION

Selenium is a trace element, at the micro level, it is essential to human and animal health, but is toxic beyond that [1]. Selenium has good industrial application. It is used in photocells, electronic, solar cells, photography, xerography, red or black glass, metal alloys, paints, dyes enamels, inks, pigments in plastic paints, textile rubber etc. Selenium sulphide used in anti-dandruff shampoo. Selenium is an antioxidant because it is embedded in glutathione peroxidases that detoxify the excess of free radicals production during oxidative stress [2-3]. The deficiency of Se in the nutrition,caused muscular dystrophy and cardiomyopathy (Keshan disease) [4].

The application of tellurium is common as additive in industrial process such as aluminum, copper, tin, arsenic, zinc, cadmium, thallium, selenium daylight lamps and electronic industry [4]. Tellurium is added to lead to improve its durability, strength and resistance to corrosion. It is used in ceramics, blasting caps, cast iron, solar panels and chalcogenide glasses. Tellurium forms a number of organometallic complexes [5].Two human deaths with 2 g of sodium tellurite injection have been reported when it was injected by mistake [6]. The fume and dust of Te can be absorbed via lung. The symptoms included garlic breath odor,

pallor, cough, shivering, sinus, tachycardia and fever with general weakness. Te has been reported as teratogen, hydrocephalus, edema, exophthalmia, ocular hemorrhage and smaller kidneys in Wistar rat fetuses (7)

Islam et al. [8] have reported that sulfur is less toxic than selenium and tellurium is more potent than selenium. Tellurium demonstrates properties similar to those of elements known to be toxic to humans and has application in industrial processes [9]. The toxicity of Se and Te is due to the reaction with –SH group to form selenotrisulphide and telenotrisulphide respectively [10-11], which are very toxic substances. There are few reports on the mechanism of toxicity of tellurium. Kaur et al. [6,12] have reported the involvement of lipids and oxidative stress on the brain in rodents.

The human is exposed to various toxicants at a time. The worker of Se and Te industries are also exposed to other toxicants. Mitochondria are a power house which provides energy to the cells. The minor change in the mitochondrial function may affect various biochemical parameters. The objective was to evaluate the combine toxicity of Se and Te in the liver mitochondria of male Wistar rats.

MATERIALS AND METHODS

Chemicals: Sodium selenite, sodium tellurite, GSSG, GSH, GR, NADPH,EDTA, DTNB, TBA, (-)-epinephrine, sodium azide, H_2O_2, sulfosalicylic acid, TCA, sucrose, mannitol, N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid and protease inhibitors were procured from Sigma-Aldrich, Germany. Caspase-3 and casapase-9 Assay Kits were imported from Biovision Incorporated, USA.

Animals and dosing

The male Wistar rats 180-200 g were taken from the animal house of Jazan University, Jazan,Kingdom of Saudi Arabia. We declare that the present study was performed according to international, national and institutional guidelines governing animal experiments studies and biodiversity rights. Five groups were made each having 8 rats. Group-1 was control and saline was given p.o and i.p. Group-2 received sodium tellurite (Te-2) 4.15 mg/kg body wt. orally [oral LD_{50} in the rat is 83 mg/kg [13] in saline (1/20 of LD_{50})] for 15 days as reported earlier [14]. Group-3 received sodium selenite (Se-2) 0.3 mg/kg body wt. i.p. in saline as reported by Zafar et al. [15]. Group-4 received sodium telluride (Te-1) 2.075 mg/kg body wt. orally + sodium selenite (Se-1) 0.15 mg/kg body wt. i.p. in saline for 15 days. Group-5 received sodium selenite (Se-2) 0.3 mg/kg body wt. i.p. in saline for 15 days.

Isolation of liver mitochondria: On day 16, animals were sacrificed and liver was dissected out. Liver mitochondria were isolated as described by Bustamante et al. [16]. The isolated mitochondria were used for the assays.

ELISA of caspase-3 and -9 activities

The apoptosis marker (caspase-3 and-9) were monitored in the liver mitochondria by using colorimetric Assay Kit and its guidelines. The results were expressed as 100% of absorbance of control.

Biochemical Assays

The lipid peroxidation was examined as per procedure of Ohkawah et al. (17) and the glutathione(GSH) was examined by the method of Jollow *et al*. [18]. The method of Mohandas *et al*. [19] was used for glutathione peroxidase(GPx) and the method of Carlberg and Mannervik [20] was used for analysis of glutathione reductase(GR). The catalase (CAT) and superoxide dismutase(SOD)were measured by the method of Claiborne [21] and Stevens *et al.* [22] respectively. The Lowery et al..[23]procedure was used to analyse the protein.

Statistics

Data were statistically analysed by using ANOVA analysis and result were represented in mean± S.E.M. The values $p< 0.05$ were considered statistically significant.

RESULTS

Effects of tellurium on the activities of caspase-3 and -9 and its protection by selenium

The caspase-3 and -9 activities were decreased considerably in Te-2 group of liver mitochondria, but there was no significant changes in these activities in Te-1+Se-1, Te-2+Se-2 and Se-2 groups except Te-1+Se-1 (caspase-3) as compared to control. The addition of Se in Te groups has protected the activities of caspase-3 and -9 significantly in the group of Te-1+Se-1,Te-2+Se-2 and Se-2 group as compared to Te-2 group (Fig. 1, 2).

Effects of tellurium on TBARS and its protection by selenium

The Te-2 has increased TBARS content significantly in the liver mitochondria as compared to the control but no change on TBARS content in the combination with Te-1+Se-1, Te-2+Se-2 or only Se-2 as compared to control group (Table-1). Both the doses of Se significantly protected the level of TBARS in the groups of Te-1+Se-1, Te-2+Se-2 and Se-2 as compared to Te-2 group.

Effects of tellurium on GSH and its protection by selenium

The Te-2 has decreased the level of GSH significantly in the liver mitochondria as compared to the control, but no change on GSH content in the combination with Te-1+Se-1, Te-2+Se-2 or Se-2group as compared to control group (Table-1). The GSH content was protected significantly in the groups of Te-2+Se-2 and Se-2 as compared to Te-2 group.

Effects of tellurium on antioxidant enzymes and its protection by selenium

The GPx, GR, SOD and catalase are endogenous antioxidant enzymes which protect the toxicity of xenobiotics. When their activities are decreased significantly, the toxicants cause more damage to the biomarkers of the organs. These enzymes activities were decreased significantly in Te-2 group as compared to control group. The treatment with both the doses of Se has elevated these enzymes activities significantly in Te-1+Se-1, Te-2+Se-2 and Se-2 groups as compared to Te-2 group.

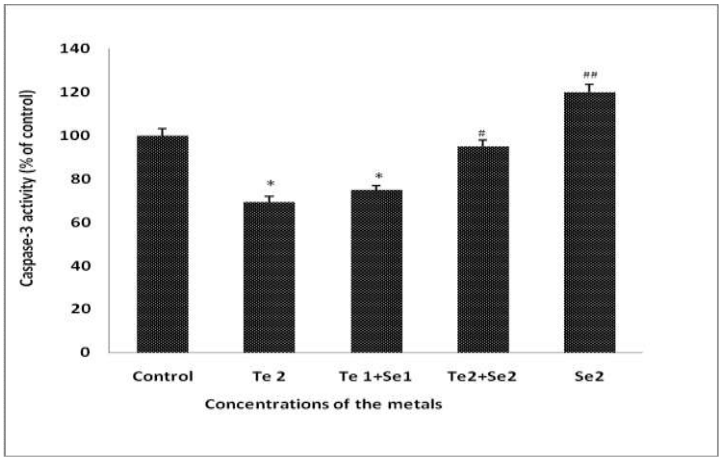

Fig. 1 Represent the Te and Se on the activity of caspase-3 in the liver mitochondria of rats.Data are expressed as mean and standard error, significance values are described as *p <0.05 vs control; #p < 0.01 vs Te-2 group; ##p < 0.001 vs Te-2 group.

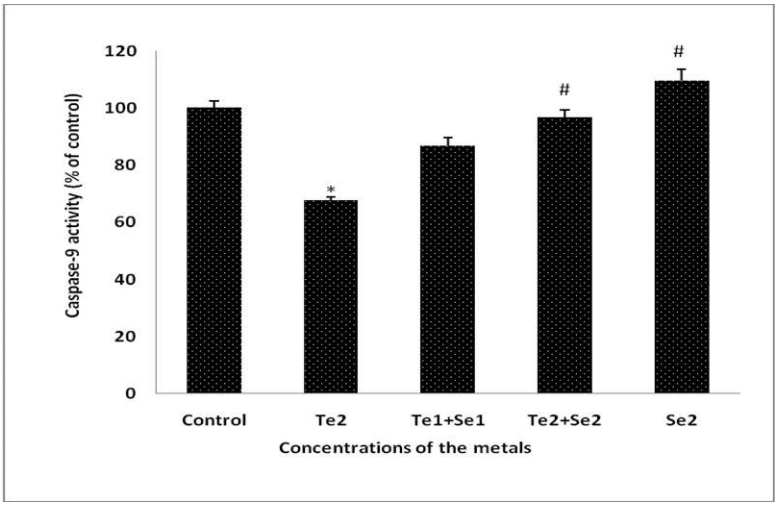

Fig. 2 shows the effect of Te and Se on the activity of caspase-9 in the liver mitochondria of rats. Data are expressed as mean and standard error, significance values are described as *p < 0.05 vs control; #p < 0.05 vs Te-2 group.

Table-1: Effects of various doses of tellurium and selenium on the activities of antioxidant enzymes (GPx, GR, SOD and catalase) in liver mitochondria of rats.

Biomarkers	Control	Te-2	Te-1+Se-1	Te-2+Se-2	Se-2
Lipid peroxidation (nmol TBARS/mg protein)	38.88±2.81	55.45±4.51*	44.49±3.11#	43.73±3.09#	38.44±2.11#
GSH (nmol/mg protein)	132.83±10.21	100.28±8.85*	116.11±9.21	121.12±10.12#	131.44±6.89#
GPx (nmol NADPH oxidized/min/mg protein)	301.42±16.3	195.31±29.02**	247.83±14.4#	262.14±13.63##	266.53±35.2##
GR (nmol NADPH oxidized/min/mg protein)	215.49±10.8	136.35±36.4*	190.52±19.9#	196.36±16.7#	198.57±12.2#
SOD (nmol epinephrine protected from oxidized /min/mg protein)	0.57±0.03	0.31±0.17*	0.40±0.04#	0.41±0.09#	0.52±0.05##
CAT (nmol H_2O_2 consumed/min/mg protein)	20.63±1.18	13.51±1.5*	19.72±0.96#	18.38±0.79#	20.55±0.96#

Note: Values are expressed as mean ± S.E.M. and significance was ascertained as *$p < 0.05$ vs control; # $p < 0.05$; ## $p < 0.01$ vs Te2 group.

DISCUSSION

The most prominent roles of mitochondria are the production of energy in the cells through the respiration and regulation of cellular metabolism. The mitochondria are power house which generates free radicals through cellular respiration. These free radicals are measured in the assay by adding thiobarbituric acid, which give a color of the complex of thiobarbituric acid reactive species/substances (TBARS) which was significantly higher in Te-2 group, suggesting that role of free radical production by Te-2. The more free radicals generated by Te-2, the more they damaged the mitochondrial function and boosted the content of LPO. Upon mixing the doses of Se with the doses of Te, the Se has quenched the production of free radicals and protected the mitochondria from damage.

GSH is an endogenous antioxidant and protects the toxicity of the xenobiotics. When xenobiotics are more toxic, these inhibit the redox cycle of GSH and GSSG due to which the formation of GSH is reduced and xenobiotics caused more damaged to the cells. The GSH is a tripeptide; γ-L-glutamyl-L-cysteinyl-glycine and has –SH group found in rich concentration inside the all organs. Se and Te are –SH reactive [24] its nature and chemistry is not clear till date[25]. The TeandSe react with –SH group and form a very toxic teleno- or seleno-trisulfide compound respectively. It has been reported that Te is more toxic than Se [8]. We hypothesized that Te react with GSH faster than Se to form teleno-trisulfide and due to this fast reaction no –SH group was available for Se to form selenotrisulfide and thus there is no toxicity of Se and it acted as an antioxidant and protected the level of GSH significantly.

The –SH group of GSH showed a crucial role in ameliorating the toxicity of peroxide attack. The membrane becomes more susceptible towards peroxide attacks if the concentration of GSH is decreased. The decreased concentration of GSH and formation of protein-glutathione mixed disulfide (PrSSG) is resulted to various membrane dysfunctions, such as inhibition of Na^+,K^+-ATPase activity [26]. The H_2O_2 is the most toxic molecule to the cells, and it is detoxified by GPx and catalase. Thus the inhibition of GSH causes the inhibition of the activities of its dependent enzymes.

Several reports are available in support of Se to restore the level of GSH and the activity of GPx, GR and CAT[15]. GPx plays an important role in scavenging the free radicals and hydroperoxides. SOD is also an important enzyme that converts superoxide into H_2O_2 [27] and catalase detoxifies H_2O_2 into H_2O. Se intake can prevent or slow down cell injury caused by imbalance between antioxidant/oxidant system i.e., oxidative stress [15, 28, 29] within the mitochondria in case of oxidative stress. Se has a dual effect on the living system (protective and toxic) because of its presence in several selenocytine or selenomethionine proteins that might be protective enzymes or substrate for capase-3. Se has a suppressive effect against DNA damage and poly-ADP-ribose polymerase (PARP) cleavage, so that, it is protective against apoptotic cell death [30-31].

The Se inhibits the mitochondrial monoamine oxidase (MAO), which supplies free radicals and potentiate the depletion of antioxidant defense system and protects the mitochondrial functions [32]. In mitochondria, the *in vivo* oxidation of MAO (auto and/or through MAO) produces peroxide and quinine derivatives during oxidative stress [33]. On the other hand, the iron catalyzes to generate •OH radicals [15] form the superoxide anion and H_2O_2. The reactive oxygen species are very reactive, which destroy the

intracellular homeostasis, affect the mitochondrial electron transport system, accelerate lipid peroxidation and finally caused cell death [15, 34].

Caspases are responsible for the disassembly of the cells during apoptosis to form apoptotic bodies. They are inactive pro-enzyme which are activated by proteolytic cleavage. The apoptotic protease activating factor-1(APAPF-1) activates caspase-9 which further activates disassembly and triggers the release of cytochrome c from mitochondria and form a complex with APAF-1 [35-36].

Caspase-3 is activated by caspase-8 and -9,that cleaves vital cellular proteins which in turn leads to cell death[37-40]. Once caspase-9 is initiated, it goes on to cleave procaspase-3 and procaspase-7 and several other cellular targeted enzymes and contents. The activation of PARP is cytotoxic which depletes the cellular NAD content, which ultimately reduces ATP synthesis. PARP also uses the ATP in their cyclic processes [41]; so for it approaches to apoptosis [13]. So many studies have reported that the oxidative stress accelerate the activity of caspase-3 and -9 [42-44], but there is no report of Te toxicity on the activation of these enzymes. This is the first report of Te toxicity on caspase-3 and -9 activities. In these findings, caspase-3 and 9 were inactivated significantly with the treatment of Te-2 as compared to control. This indicates that Te has different mechanism(s) than oxidative stress in in the inactivation of caspases. Se and PARP is required as a substrate for caspases activity, so treating the animals with Se has activated the activity of caspases in mitochondria. There is no report of Te toxicity on PARP. Does the inhibition of PARP play a major role in the activity of caspase-3 and -9? Further a detail study of Te toxicities on the apoptosis pathways, release of cytochrome c and PARP activity will be required to understand the mechanism(s) of action of Te on apoptosis in the liver mitochondria.

CONCLUSION

Selenium,is an important trace element which is commonly present in our daily diet that might be the best tool for the treatment of Te toxicity.

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