



The Protective Effect of Selenium on T-2-Induced Nephrotoxicity Is Related to the Inhibition of ROS-Mediated Apoptosis in Mice Kidney

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Abstract

T-2 toxin is produced by the *Fusarium* genus. Ingestion of food or feed contaminated by T-2 toxin will cause damage to kidney. Selenium (Se), an essential trace element, showed the significant protective effects against kidney and renal cell damage induced by toxic substances. To explore the protective effects and mechanisms of Se against T-2-induced renal lesions, forty-eight male Kunming mice were exposed to T-2 toxin (1.0 mg/kg) and/or Se (0.2 mg/kg) for 28 days. In this study, we found that Se alleviated T-2-induced nephrotoxicity, presenting as increasing the body weight and kidney coefficient, relieving the renal structure injury, decreasing the contents of renal function-related biomarkers, decreasing the levels of reactive oxygen species (ROS), and increasing the mitochondrial membrane potential in T-2 toxin-treated mice. In addition, inhibition of renal cell apoptosis by Se was associated with blocking the mitochondrial pathway in T-2 toxin-treated mice, presenting as decreasing the protein expression of cytochrome-c, activities of caspase-3/9, as well as regulating the protein and mRNA expressions of Bax and Bcl-2. These results documented that the alleviating effect of Se on T-2-induced nephrotoxicity is related to the inhibition of ROS-mediated renal apoptosis.

Keywords Se · T-2 toxin · ROS · Apoptosis · Kidney

Abbreviation

Se	Selenium
BW	Body weight
ROS	Reactive oxygen species
MMP	Mitochondrial membrane potential
Cyt-c	Cytochrome-c
TEM	Transmission electron microscope
GSG-Px	Glutathione peroxidase

Introduction

Mycotoxin contamination is a worldwide food safety problem. According to the Food and Agriculture Organization of

the United Nations (FAO), about 25% of the world's grains and 1 billion metric tons of food may be contaminated by mycotoxins, causing serious economic losses [1]. As a type A trichothecene mycotoxin, T-2 toxin is one of the most harmful toxins to the health of humans and animals [2]. T-2 toxin can be transmitted through food chain and is a risk factor for human fatal alimentary tract toxic Aleutian and Kashin Beck disease [3]. The kidney is one of the target organs of T-2 toxin [4–8]. The toxic effect of T-2 toxin is associated with the production of reactive oxygen species (ROS). T-2 toxin can cause excessive ROS production and disturb the cellular redox balance and result in kidney damage [9]. Mitochondria is the target of ROS, and the high level of ROS in mitochondria can attack the phospholipids in the cell membrane, then lead to the depolarization of mitochondrial membrane, cause caspases cascade, and finally trigger mitochondrial apoptosis [10]. Excessive apoptosis can destroy the structure of normal cells and lead to dysfunction [8, 11, 12]. T-2 toxin can induce the apoptosis in kidney and renal cell lines [8, 12, 13]. Thus, excessive ROS and apoptosis are the pathological basis of renal injury induced by T-2 toxin.

As a human body essential trace element, selenium (Se) is a functional component of several enzymes (glutathione peroxidases, selenoprotein P, and thioredoxin reductases) with

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physiological antioxidant properties [14], which can effectively remove oxygen free radicals, protect organs and tissues from oxidative damage and apoptosis [15]. Se can play a protective role in kidney and renal cell damage induced by various poisons by increasing the expression of selenase in organism, clearing ROS, and inhibiting cell apoptosis [10, 16–18]. However, there are few studies on Se alleviating the renal damage caused by T-2 toxin. The only study showed that feeding the diet containing 0.2 mg/kg organic Se for 21 days can significantly alleviate the oxidative stress, the inflammatory response, and pathological damage of rabbit kidney caused by 0.4 mg/kg T-2 toxin, which proves that Se has protective effect on oxidative damage and inflammation of rabbit kidney caused by T-2 toxin; meanwhile, the kidney injury was alleviated [9]. Moreover, inflammation can induce apoptosis, when inflammation occurs, the increase of pro-inflammatory cytokines will induce apoptosis and further aggravate the development of the disease [19–22]. While it is not clear whether Se can alleviate the apoptosis induced by T-2 toxin. This research aimed to explore whether the protective effect of Se on T-2-induced nephrotoxicity is related to the inhibition of ROS-mediated apoptosis. It is hoped to provide theoretical basis and new approaches for the prevention and treatment of T-2 nephrotoxicity.

Materials and Methods

Animals and Experimental Design

All mice were housed in the Biomedical Research Center, and the procedures were approved by the Animal Ethics Committee (Northeast Agricultural University, China). The house has a 22–24 °C temperature, 50–60% relative humidity, and a 12/12-h light/dark cycle. All animals were provided standard pellet diet (Xietong Organism, China) and distilled water ad libitum. The composition of the diet is shown in the text of the supplementary information TEXT S9.

After 7 days of acclimatization, forty-eight male Kunming mice (6 weeks old) were divided into four groups ($n = 12$): control group (CG, 0.0 mg/kg/day T-2 toxin and 0.0 mg/kg/day Se), T group (TG, 1.0 mg/kg/day T-2 toxin and 0.0 mg/kg/day Se), Se + T-2 group (STG, 1.0 mg/kg/day T-2 toxin and 0.2 mg/kg/day Se), and Se group (SG, 0.0 mg/kg/day T-2 toxin and 0.2 mg/kg/day Se). The STG were treated with Se at 0.2 mg/kg 2 h prior to T-2 toxin administration, and then given T-2 toxin at 1.0 mg/kg. T-2 toxin ($\geq 99.8\%$, Pribolab, China) was dissolved in distilled water containing 4% v/v ethanol, Na_2SeO_3 ($\geq 98\%$, Sigma, USA) in the STG was dissolved in distilled water, and SG was dissolved in distilled water containing 4% v/v ethanol [23]. The CG was gavage daily with distilled water containing 4% v/v ethanol. The mice were treated by oral gavage for 28 days and sacrificed on the 29th day [24]. To maintain a constant

intake of T-2 toxin and Se, the body weight (BW) of mice was measured every day and adjusted the dose accordingly. The T-2 toxin dose in this study was in accordance with that of oral LD_{50} in mice (10.0 mg/kg BW) [25], and the supplementation of Se (Na_2SeO_3) is based on the Chinese Dietary Reference Intakes (DRIs) and non-toxic in rodents [26]. All animal procedures were performed in accordance with the Guidelines for Care and Use of Laboratory Animals [27] and approved by the Animal Ethics Committee of Northeast Agricultural University, China. During the experimental period, the health status of mice was monitored daily and no animal died in all the treatment groups.

Sample Preparation

At the end of this study, the mice BW was recorded first. The mice were sacrificed after anesthetization by intraperitoneal injection with 1% pentobarbital (5 mL/kg) and tissue samples retrieved. Next, the serum was obtained from the whole blood (700 μL) by centrifugation at 3000 rpm for 10 min to detect the contents of biochemical indexes of renal function. Kidney tissues were excised immediately and washed in ice-cold saline. Parts of the kidneys were taken out for ultrastructure observation. The rest of kidneys were weighted and stored at -80 °C for measuring other parameters.

The Histopathological Observation of Kidney

The histopathological lesions of kidney were observed according to the previous study [28]. The specific steps are shown in the text of the supplementary information TEXT S1.

The Ultrastructure Observation of Kidney

The ultrastructure of kidney was observed by transmission electron microscope (TEM) according to the previous study [29]. The specific steps are shown in the text of the supplementary information TEXT S2.

The Analysis of BUN, SCR, Cys-C, and β_2 -Mg Contents

The renal function biomarkers were detected by automatic blood analyzer (AU680 Beckman Coulter, Inc., USA) as markers of renal dysfunction.

Determination of Oxidative Stress Markers in the Kidney

The ROS and glutathione peroxidase (GSH-Px) of kidney were observed according to the research of Zhou et al. [10]. The specific steps are shown in the text of the supplementary information TEXT S3.

Detection of Kidney Apoptosis

The kidney apoptosis was observed by TUNEL staining according to the previous study [29]. Positive staining was detected by Image-Pro Plus 6.0 software. The specific steps are shown in the text of the supplementary information TEXT S4.

Determination of MMP in the Kidney

The MMP of kidney was observed according to the research of Yu et al. [30]. The specific steps are shown in the text of the supplementary information TEXT S5.

Measurement of Activities of Caspase-3 and Caspase-9 of Kidney

The activities of caspase-3 and caspase-9 observation were measured using kits (C1116, C1158, Beyotime, China). The specific steps are shown in the text of the supplementary information TEXT S6.

Determination of the Protein Expression in Kidney

Protein was extracted by kit, and the concentration was determined by BCA method (P0010S, Beyotime, China). The specific steps are shown in the text of the supplementary information TEXT S7.

Determination of Gene Expression in the Kidney

The mRNA expression of Bcl-2, Bax, and cytochrome-c (Cyt-c) were detected by qRT-PCR (Table 1). The specific steps are shown in the text of the supplementary information TEXT S8.

Statistical Analysis

All the data were presented as mean \pm standard deviation (mean \pm SD). The data were analyzed by one-way ANOVA and LSD test was used as the post hoc test (SPSS 22.0 software; SPSS Inc., Chicago, IL, USA). In all statistical comparisons, * $P < 0.05$ and ** $P < 0.01$ symbols indicated significant differences compared

with the CG. # $P < 0.05$ and ## $P < 0.01$ symbols indicated significant differences compared with the TG.

Results

Se Protects Against the T-2-Induced Reduction of BW and Kidney Coefficient

Compared to the CG, the BW and kidney coefficient were decreased in the TG ($P < 0.05$, $P < 0.01$). However, these changes were significantly alleviated in the STG as compared to the TG ($P < 0.05$). There were no significant difference between SG and CG (Fig. 1).

Se Alleviates T-2-Induced Renal Structural Damage

In H&E staining, the intact glomeruli and well-arranged, compact tubules were observed in the CG. The destruction of renal tubular structure and the detachment of renal tubular nuclei were observed in the TG. However, these changes were significantly alleviated in the STG as compared to the TG. In addition, treatment with Se along did not cause damage to renal structure, which was similar to the CG in morphology (Fig. 2).

Se Alleviates T-2-Induced Ultrastructure in Kidney

TEM examination indicated that normal ultrastructure of renal epithelial cells was found in the CG, with the normal mitochondria and intact cell membrane and nuclear membrane. Swelling of mitochondria, loss of mitochondrial cristae, and vacuolation of mitochondria were observed in the TG. However, these changes were significantly alleviated in the STG as compared to the TG. There were no significant difference between SG and CG (Fig. 3).

Se alleviates T-2-Induced Renal Dysfunction in Kidney

Compared to the CG, the contents of BUN, SCR, Cys-C, and β 2-Mg were increased in the TG ($P < 0.01$). However, these

Table 1 Primer sequence and length of destination

Genes	Gene numbers	Primer sequences	Primer lengths(bp)	Product lengths(bp)
Bax	NM_017059.2	UP: 5' GCTAGCCTGGTGCAAGATACT 3'	21	178
		LOW: 5' TGGGGGCCAGTATTGCATTT 3'	20	
Bcl-2	NM_016993.1	UP: 5' GCTAGCCTGGTGCAAGATACT 3'	20	119
		LOW: 5' TGGGGGCCAGTATTGCATTT 3'	20	
Cyt-c	NM_007808.5	UP: 5' ACCAGCCCGGAACGAATTA 3'	21	135
		LOW: 5' CCGAACAGACCGTGGAGATT 3'	20	
β -Actin	NM_007397.5	UP: 5' GTTGAGCAAACATCCCCCA 3'	20	187
		LOW: 5' ACGCGACCATCCTCTCTTA 3'	20	

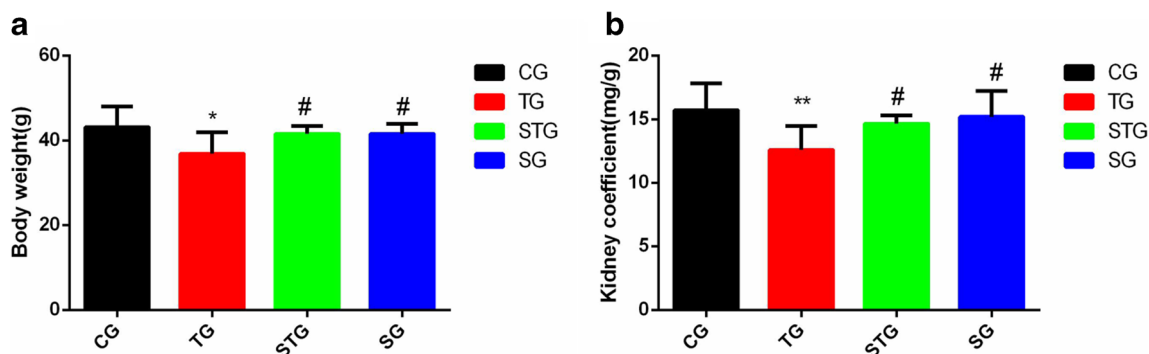


Fig. 1 The effects of Se on BW and kidney coefficient from mice exposed to T-2 toxin. **a** BW. **b** Kidney coefficient. All data were expressed as mean \pm SD. * $P < 0.05$ and ** $P < 0.01$ indicate the

significance of differences versus the CG. # $P < 0.05$ and ## $P < 0.01$ indicate the significance of differences versus the TG. CG control group, TG T-2 group, STG Se + T-2 group, SG Se group

changes were significantly alleviated in the STG as compared to the TG ($P < 0.01$). There were no significant difference between SG and CG (Fig. 4).

Se Alleviates T-2-Induced the Oxidative Stress in Kidney

The contents of ROS were increased in the TG compared to the CG ($P < 0.05$). The activity of GSH-Px was decreased in the TG compared to the CG ($P < 0.01$). However, these changes were significantly alleviated in the STG as compared to the TG ($P < 0.05$, $P < 0.01$). There were no significant difference between SG and CG (Fig. 5).

Se Alleviates T-2-Induced Apoptosis

TUNEL Staining Assay

The TUNEL-positive staining nuclei were not found in the CG. The percentage of TUNEL-positive nuclei significantly increased in the TG as compared to the CG ($P < 0.01$). However, these changes were significantly alleviated in the STG as compared to the TG ($P < 0.01$). There were no significant difference between SG and CG (Fig. 6a, b).

TEM Observation of Apoptosis

The normal nuclear structure and chromatin distribution were found in the CG. The nuclear membrane shrunk, and chromatin condensed under the nuclear membrane was observed in the TG compared to the CG. However, these changes were significantly alleviated in the STG as compared to the TG. There were no significant difference between SG and CG (Fig. 6c).

Measurement of MMP

The MMP levels were decreased in the TG as compared to the CG ($P < 0.01$). However, these changes were significantly alleviated in the STG as compared to the TG ($P < 0.05$). There were no significant difference between SG and CG (Fig. 6d).

Se Alleviates T-2-Induced Apoptosis via Mitochondria Pathways in Kidney

Se Alleviates the T-2-Caused Induction of Activities of Caspase-3 and Caspase-9 in Kidney

T-2 toxin treatment significantly increased the activities of caspase-3 and caspase-9 ($P < 0.01$). However, these changes were significantly alleviated in the STG as compared to the

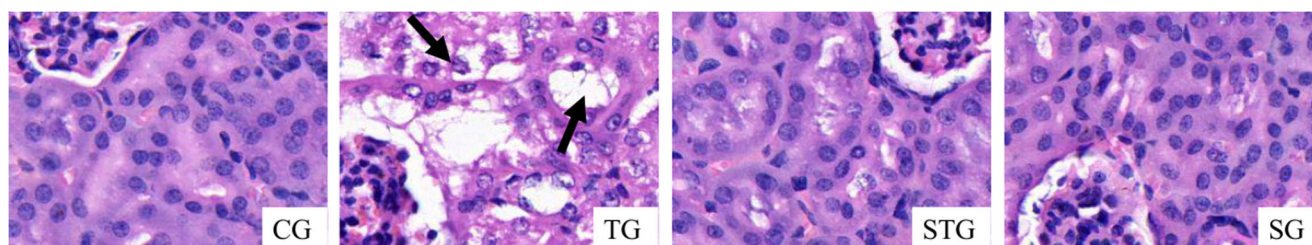


Fig. 2 The effects of Se on renal structural damage in kidney from mice exposed to T-2 toxin. H&E staining of kidney in mice (magnification, $\times 400$). The “black arrow” showed the destruction of renal tubular structure

and the detachment of renal tubular nuclei. CG control group, TG T-2 group, STG Se + T-2 group, SG Se group

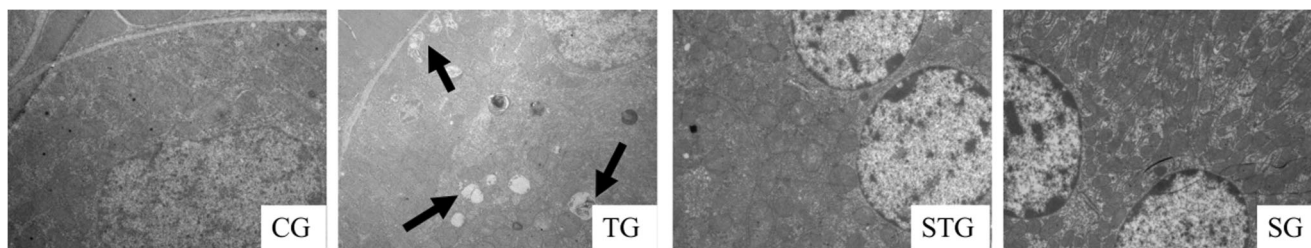


Fig. 3 The effects of Se on renal ultrastructure and function damage in kidney from mice exposed to T-2 toxin. Representative photomicrographs of renal tubular cells ultrastructure (magnification, 8000 \times). The

“black arrow” showed the mitochondria lesions. CG control group, TG T-2 group, STG Se + T-2 group, SG Se group

TG ($P < 0.01$). There were no significant difference between SG and CG (Fig. 7a, b).

compared to the TG ($P < 0.01$); there were no significant difference between SG and CG (Fig. 7c–i).

Effects of Se on mRNA and Protein Expressions of Bax, Bcl-2, and Cyt-c in Kidney

The mRNA and protein expressions of Bax were significantly increased in the TG as compared to the CG ($P < 0.01$), and the mRNA and protein expressions of Cyt-c were significantly increased in the TG and STG as compared to the CG ($P < 0.05$, $P < 0.01$), whereas they were markedly decreased in the STG as compared to the TG ($P < 0.05$, $P < 0.01$); there were no significant difference between SG and CG. The mRNA and protein expressions of Bcl-2 were significantly decreased in the TG and STG as compared to the CG ($P < 0.05$, $P < 0.01$), whereas it was markedly decreased in the STG as

Discussion

Numerous studies have reported that the T-2-induced toxicity was related to oxidative stress [10, 15]. Antioxidant therapy is considered to be an important way to interfere with T-2 toxicity. Se, well known as an essential trace element, has been reported to provide protection from ROS-induced cell damage [15, 31–33]. Se pretreatment can diminish ROS and cell apoptosis induced by various toxic substances [18, 32, 34]. In this study, we aim to clarify whether the protective effect of Se on T-2-induced nephrotoxicity is related to the inhibition of ROS-mediated apoptosis.

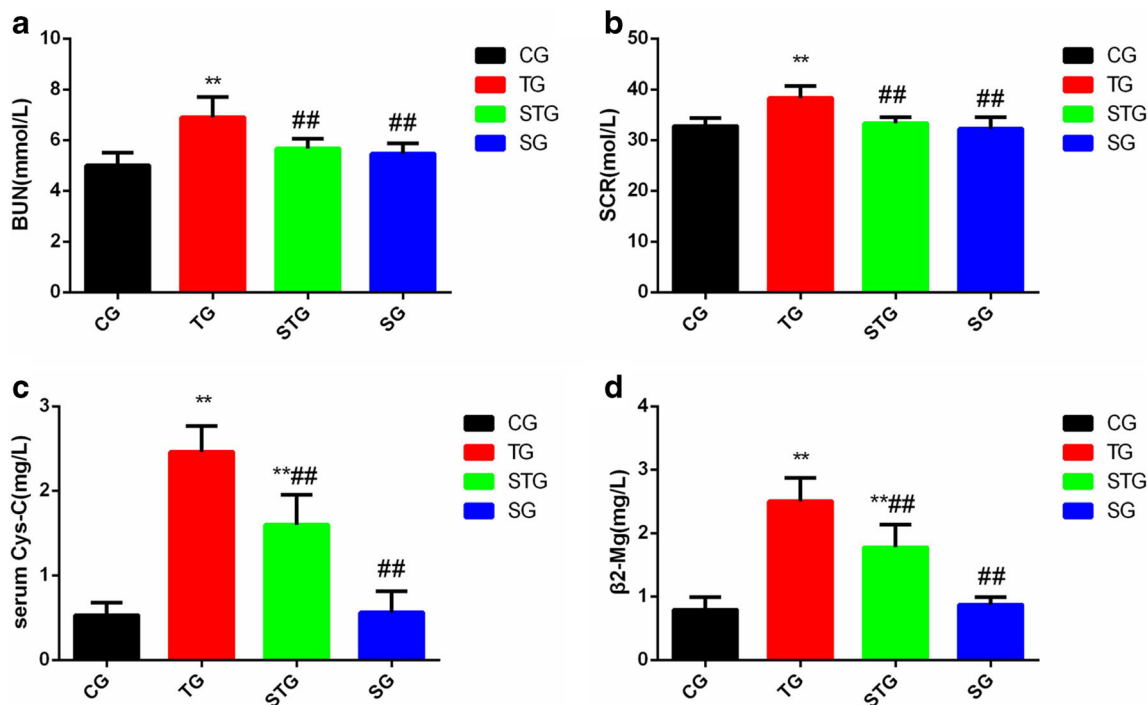


Fig. 4 The effects of Se on renal dysfunction in kidney from mice exposed to T-2 toxin. **a** BUN. **b** SCR. **c** Cys-C. **d** β 2-Mg. All data were expressed as mean \pm SD. * $P < 0.05$ and ** $P < 0.01$ indicate the

significance of differences versus the CG. # $P < 0.05$ and ## $P < 0.01$ indicate the significance of differences versus the TG. CG control group, TG T-2 group, STG Se + T-2 group, SG Se group

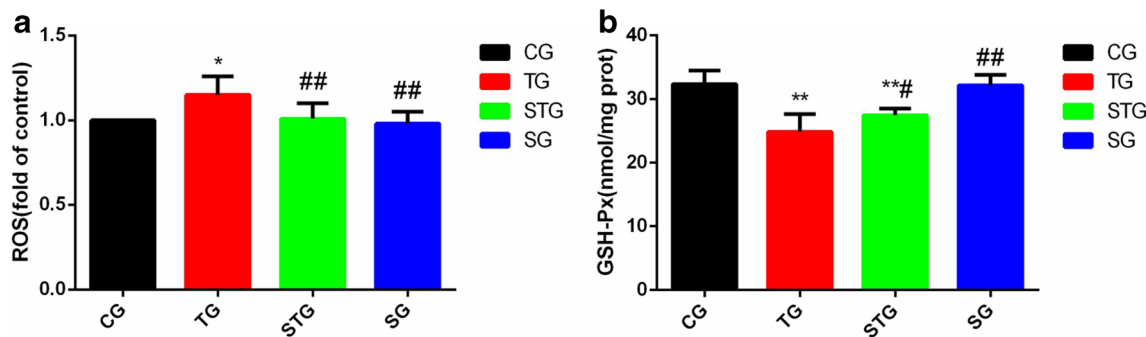


Fig. 5 The effects of Se on ROS and GSH-Px in kidney from mice exposed to T-2 toxin. All data were expressed as mean ± SD. **P* < 0.05 and ***P* < 0.01 indicate the significance of differences versus the CG. #*P*

< 0.05 and ##*P* < 0.01 indicate the significance of differences versus the TG. CG control group, TG T-2 group, STG Se + T-2 group, SG Se group

The kidney is essential for maintaining normal body function, which can regulate the liquid electrolyte and acid-base balance and create a stable environment for the metabolism of tissues and cells [35]. Thus, kidney injury is often related to renal dysfunction and increased risk of death. Se exerted the positive effect on BW reduction induced by streptozotocin in male Wistar rats [36], and kidney coefficient reduction induced by cadmium in ICR male mice [15]. We found Se

remarkably ameliorated T-2 toxin induced reduction in the BW and kidney coefficient. Se positively affects feed utilization through participation in the metabolism of carbohydrates, lipids, and proteins [37], which play an important role in improving the BW and organ coefficient of mice. By histopathological examination, Se pretreatment diminished T-2-induced tubular lesions. To further evaluate the ameliorative effect of Se on T-2-induced structure lesion of kidney, the

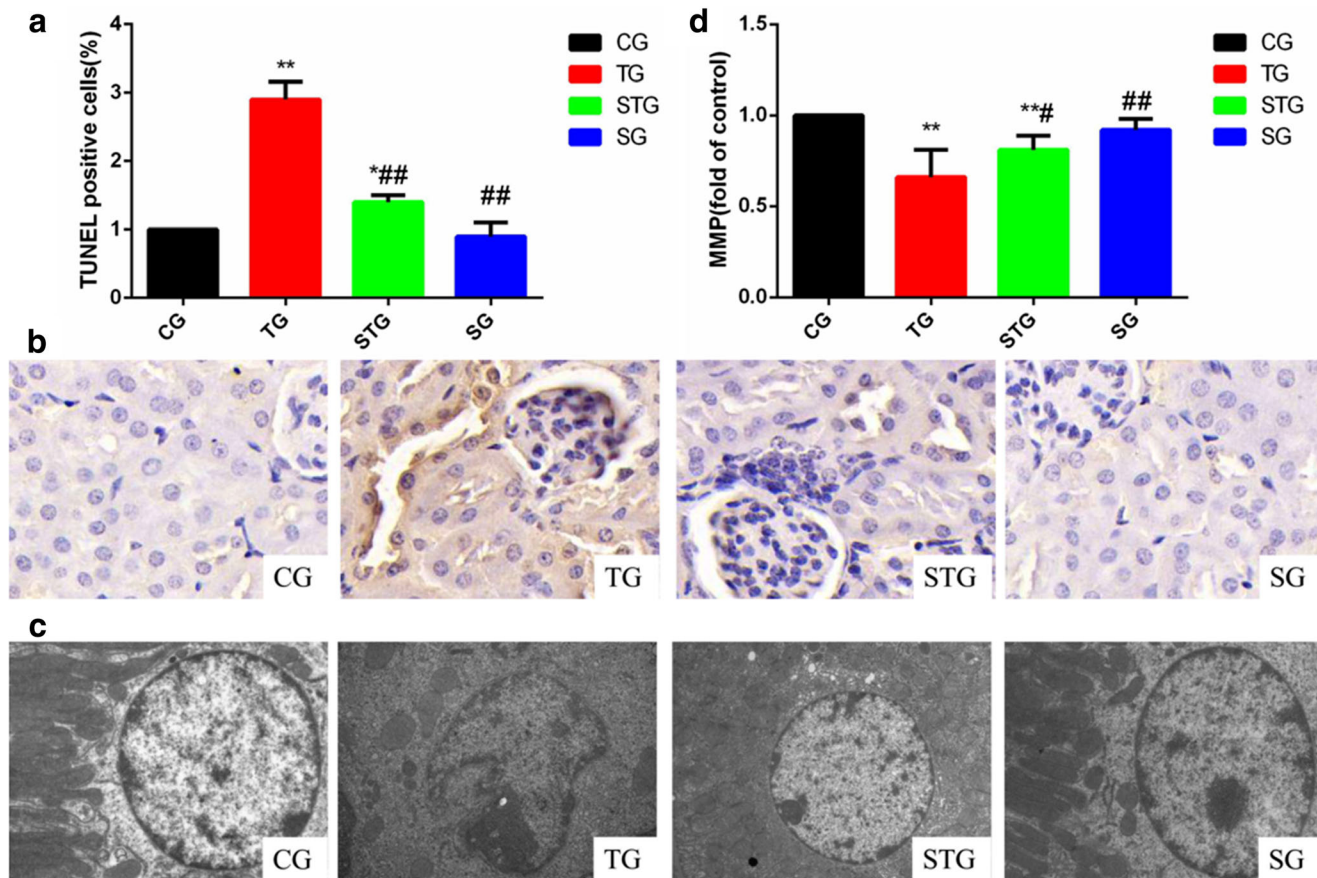


Fig. 6 The effects of Se on apoptosis in kidney from mice exposed to T-2 toxin. **a** The percentage of TUNEL-positive cells. **b** TUNEL staining (magnification, × 400). **c** Representative photomicrographs of renal tubular cell nucleus ultrastructure (magnification, × 20,000). **d** Relative MMP

level. All data were expressed as mean ± SD. **P* < 0.05 and ***P* < 0.01 indicate the significance of differences versus the CG. #*P* < 0.05 and ##*P* < 0.01 indicate the significance of differences versus the TG. CG control group, TG T-2 group, STG Se + T-2 group, SG Se group

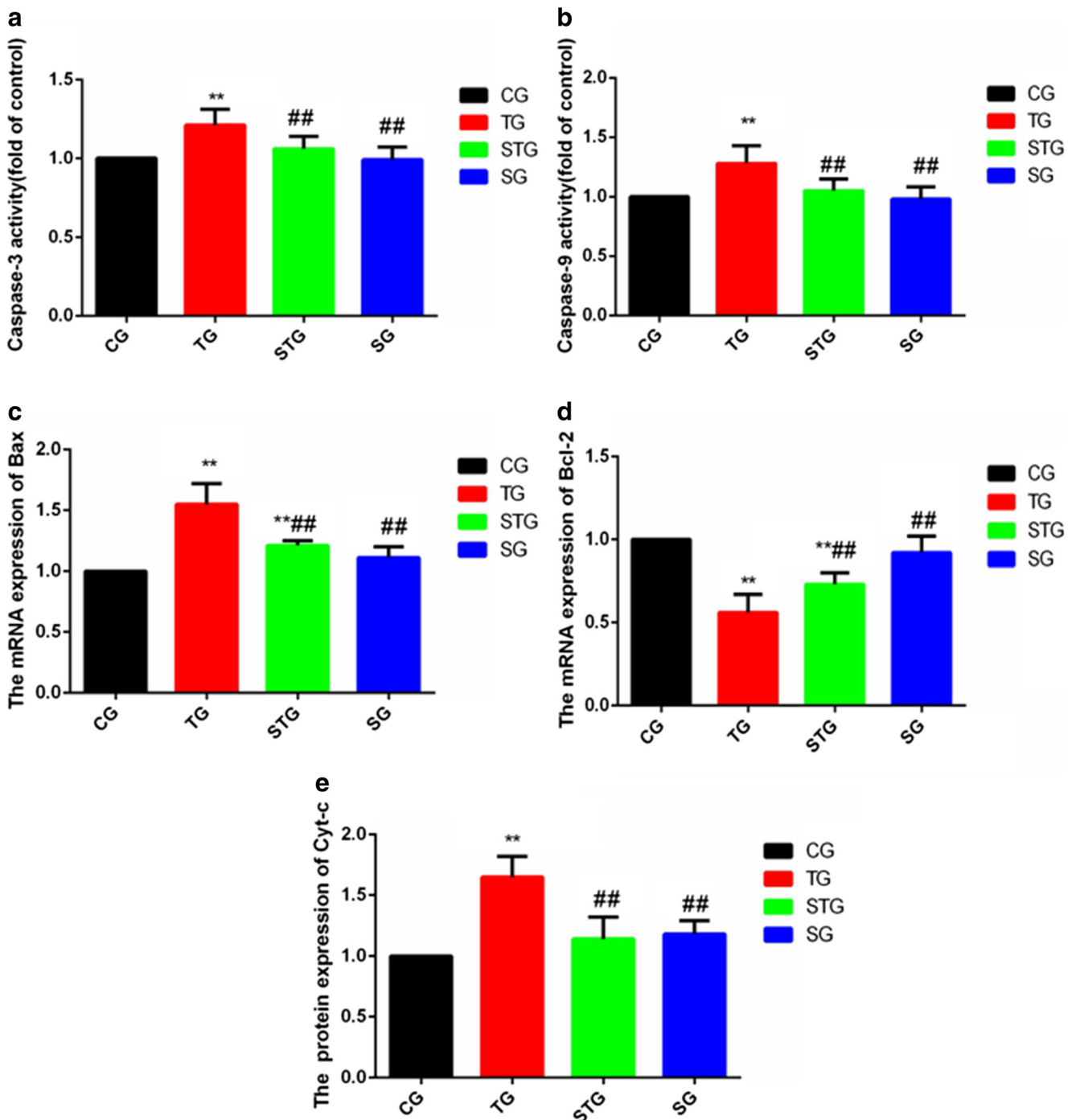


Fig. 7 The effects of Se on mitochondrial apoptosis pathways in kidney from mice exposed to T-2 toxin. **a, b** The activities of caspase-3 and caspase-9. **c–e** The mRNA expressions of Bax, Bcl-2, and Cyt-c. **f** Representative image of Bax, Bcl-2, and Cyt-c. **g–i** The protein expressions of Cyt-c, Bax, and Bcl-2. All data were expressed as mean \pm SD. * P

< 0.05 and ** $P < 0.01$ indicate the significance of differences versus the CG. # $P < 0.05$ and ## $P < 0.01$ indicate the significance of differences versus the TG. CG control group, TG T-2 group, STG Se + T-2 group, SG Se group

ultrastructure of kidney was observed by TEM, we found that pretreatment with Se markedly antagonized T-2-induced swelling of mitochondria, loss of mitochondrial cristae, and vacuolation of mitochondria. The possible reason is that Se is

a component of many selenoproteins with redox function [38], which plays an important role in redox regulation, thus protecting the integrity of cell membrane [39], participating in the repair of damaged kidney tissue and protecting the

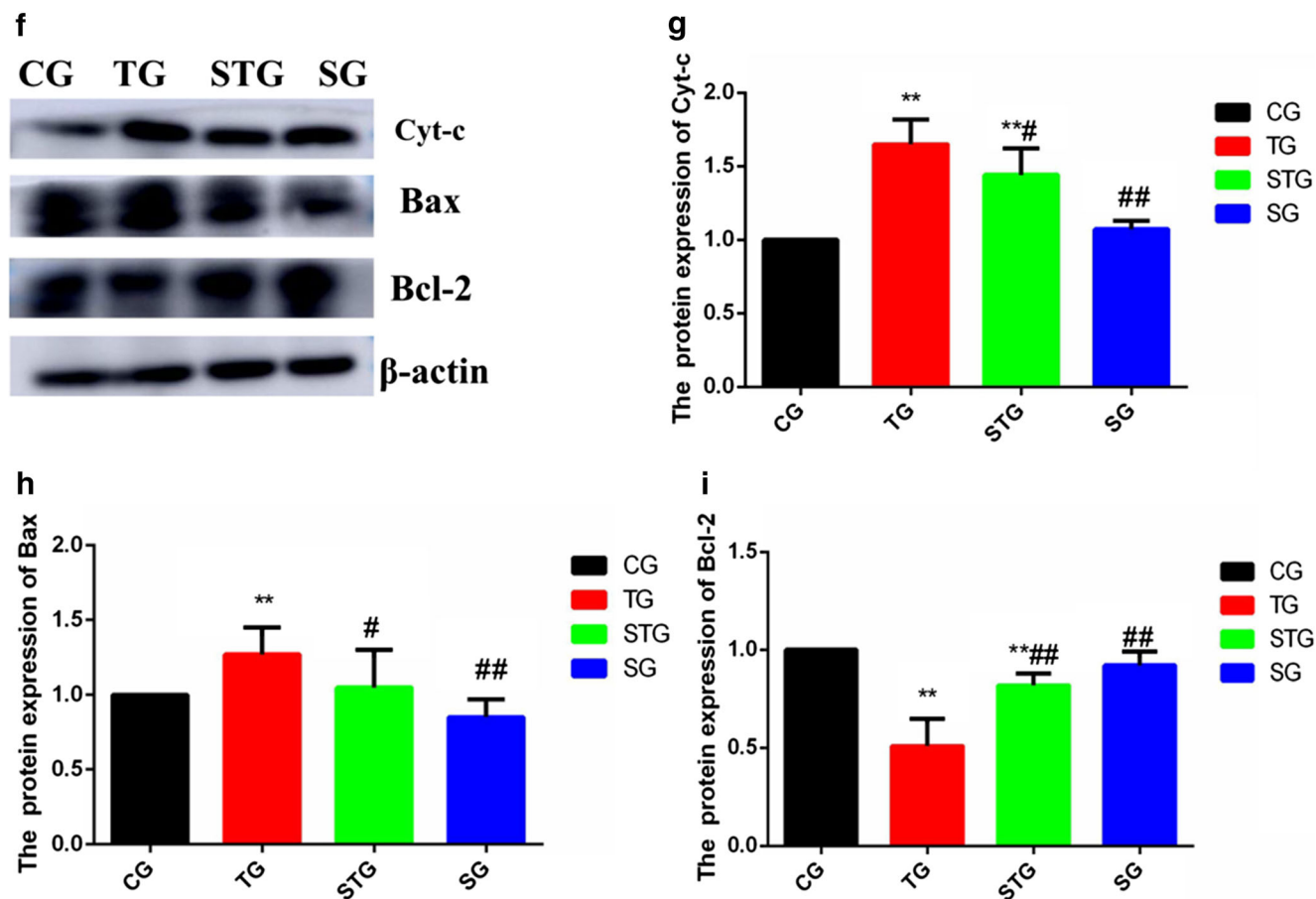


Fig. 7 (continued)

structure of kidney [40]. These results indicated that Se can alleviate the damage of renal structure and the kidney development inhibition caused by T-2 toxin. BUN and SCR can be used as indicators of acute renal tubular lesions, and serum Cys-C and β 2-Mg can be used as indicators of glomerular filtration function [28, 41]. Pretreatment with Se significantly diminished the renal dysfunction of streptozotocin-exposed rats and cadmium-exposed mice [15, 36]. We found that Se pretreatment can reduce the T-2-induced increase of renal function biomarkers, suggesting that Se can antagonize the renal dysfunction induced by T-2 toxin.

Apoptosis is called programmed cell death, which can remove defective cells from the body to ensure the health of multicellular organisms. However, excessive apoptosis will cause cell death and nephrotoxicity [29, 42, 43]. In our study, the results of TUNEL staining and the TEM observation proved that T-2 toxin induced the excessive apoptosis in the kidney, which is similar to the results of heavy metal-exposed mice and chicken [15, 16], while pretreatment with Se attenuated the apoptosis. ROS is mainly produced in mitochondria, and elevated ROS levels will destroy the normal structure of cells, leading to dysfunction. Moreover, ROS is closely related to mitochondrial membrane damage, which can lead to cell

apoptosis [44]. Se is involved in the formation of GSH-Px enzyme, which plays an important role in the elimination of ROS [45]. Se attenuated the production of ROS and the decrease of activity of GSH-Px in ochratoxin A-treated porcine kidney epithelial cells and fluorine-treated broiler kidney [18, 32]. In this study, Se administration dramatically attenuated T-2-induced production of ROS and the decrease of activity of GSH-Px. Se plays an important role in human and animal, which neutralizes, eliminates, and blocks the synthesis of ROS, and Se could eliminate ROS through antioxidant GSH-Px [32, 46, 47]. Therefore, we speculate that ROS production may be involved in renal dysfunction and excessive apoptosis caused by T-2 toxin, while Se improves normal renal structure and function and prevents apoptosis by eliminating excessive ROS. Mitochondria are the major source of ROS production in cells, in turn, the most adversely affected organelles; excessive ROS can result in mitochondrial dysfunction [48, 49]. MMP plays a key role in mitochondrial homeostasis by selectively eliminating dysfunctional mitochondria. It is also the driving force for the transport of ions and proteins, which are essential for the healthy function of mitochondria. The continuous decrease or increase of MMP may lead to unnecessary loss of cell viability and various

pathological changes [50]. Apoptosis is closely related to the stability of MMP, when MMP collapses, apoptosis is irreversible [51, 52]. The collapse of MMP can lead to apoptosis of normal cells through mitochondrial pathway [53]. We found pretreatment with Se ameliorated T-2-induced MMP collapse. A similar antagonistic effect of Se has been found in the NaF-treated rat kidney cells (NRK-52E) and cadmium-treated ICR male mice kidney [15, 54]. Therefore, it is suggested that Se may protect the kidney by restoring the normal level of MMP and then reducing abnormal apoptosis. When oxidative stress occurs, ROS is produced in large quantities and then attack of membrane phospholipids, the decrease of MMP leads to biochemical changes inside and outside of the mitochondrial membrane, which makes Cyt-c release into the cytoplasm and binds to apoptotic protease activating factor-1 (Apaf-1). When activated Apaf-1 forms apoptosome, it binds and cleaves initiator procaspase-9, and converts it to an active form (caspase-9), then turns the caspase-3 into active cleaved form (cleaved caspase-3) and triggers mitochondrial apoptosis [55]. We found T-2 toxin exposure caused the increase of protein expression of Cyt-c, activities of caspase-3 and caspase-9, while pretreatment with Se alleviated the above changes. Our study confirmed that T-2 toxin decreased MMP and led to the release of Cyt-c into the cytoplasm, which upregulated the activities of caspase-3/9 and promoted apoptosis. Se indirectly regulated the Cyt-c and caspase-3/9 by alleviating the decline of MMP, and finally alleviated apoptosis. Bcl-2 is the first member identified as an antiapoptotic protein. Bax is known as the proapoptotic protein in Bcl-2 family proteins. In the presence of apoptotic stimuli, the expression of Bax increased, and then combined with Bcl-2 to activate caspase cascade to induce apoptosis [56]. Se has a protective effect on oxidative stress and mitochondrial apoptosis induced by cadmium in mice kidney, presenting as blocking ROS production, inhibiting MMP collapse, the Cyt-c release, and caspase activation, and changing the levels of Bcl-2 and Bax [15]. We found T-2 exposure caused the increase of protein and gene expression of Bax, and the decrease of protein and gene expression of Bcl-2, while pretreatment with Se alleviated the above changes. Bcl-2 family members also act as central executors of apoptotic pathways by controlling the release of Cyt-c from mitochondria into the cytosol and activating caspase-3 [57–59]. Therefore, we speculate that Se may regulate the MMP and protein expressions of Bcl-2 family, so as to control the release of Cyt-c and regulate the activities of caspase-3/9, and finally alleviate the apoptosis induced by T-2 toxin. These results displayed that the mitigation of Se on T-2-induced excessive apoptosis of kidney is related to the mitochondrial apoptosis pathway. The above results showed that antiapoptosis may be one of the beneficial mechanisms of Se against T-2 nephrotoxicity.

Conclusion

In summary, the alleviating effect of Se on T-2-induced renal lesion is related to the ROS-mediated apoptosis. These results suggest that Se can be used as a dietary additive against the toxicity of T-2 toxin.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12011-021-02614-4>.

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Declarations

Conflict of Interest The authors declare no competing financial interest

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