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Modulatory Effect of Ginseng Extracts against Trafos Cu Plant Growth Regulators Induced Renal Toxicity in Rats

Sarah Alashmouni[1], Afaf El-Atrash[1], Ehab Tousson[1], Amira Saber Ahmed[2]

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ABSTRACT

Background: Plant growth regulators (PGRs) are widely used as pesticides that can induce toxicity to industrial workers and farmers directly by inhalation during use in agriculture and indirectly through food that have been sprayed with PGRs. Therefore, this work intends to investigate the protective and therapeutic effects of ginseng extracts against Trafos Cu induced kidney toxicity, DNA fragmentation, oxidative stress, and PCNA expression alterations.

Methods: A total of 60 male rats divided into 6 groups [Gp1, control; Gp2, ginseng; Gp3, Trafos Cu; Gp4, Ginseng+ Trafos Cu; Gp5, Trafos Cu+Ginseng; Gp6, Self-treated.

Result: Current findings revealed that rats treated with Trafos Cu (Gp3 & Gp6) induced a significant elevation in serum urea, creatinine, sodium, potassium, chloride and renal injury, DNA damage, MDA, PCNA, TNFá expressed and a significant depletion in calcium, GSH, and catalase levels as compared to control. Treatments of Trafos Cu with Ginseng (Gp4 & Gp5) induced improvements in kidney functions and structure with best results for Gp5. Ginseng has the capacity to mitigate the renal toxicity induced by Trafos Cu in male albino rats.

Key words: Ginseng, Kidney toxicity, Oxidative stress, PCNA, PGRs Trafos Cu, TNFα expressions.

INTRODUCTION

Plant growth regulators (PGRs) are currently one of the widely used pesticides, as being considered to have relatively low toxicity compared with other pesticides (Sumathi *et al*., 2017; Tousson *et al*., 2020; Wang and Hao, 2023). Exposure to PGRs are linked to many forms of toxicity that impact multiple organs in our body including neurotoxicity, hematological, hepatotoxicity, carcinogenicity, nephrotoxicity, genotoxicity and teratogenicity (Abd Eldaim *et al*., 2019; Boukerche *et al*., 2024; Sahoo *et al*., 2024). A variety of PGRs are utilised in agriculture including calcium carbide, acetylene, ethylene, propylene and Trafos Cu. Trafos Cu is PGRs used in agriculture that affects industrial and agricultural workers directly and indirectly (Abdel Megeed *et al*., 2021).

Numerous natural products can be used to treat a variety of illnesses (Tousson *et al*., 2022; Radwan *et al*., 2023; Hasan *et al*., 2024). Ginseng is widely used as an alternative medicine in Chinese and Korean cuisines and as a natural therapy for the prevention and/or treatment of a variety of ailments, as it has anti-aging, anti-allergic, anti-pyretic and immunostimulant activities (Majid, 2019; Liu *et al*., 2022). Consequently, this study intends to investigate the protective and therapeutic effects of ginseng extracts against Trafos Cu-induced kidney toxicity, DNA fragmentation, oxidative stress, TNFα and PCNA expression changes in male rats.

MATERIALS AND METHODS

Chemical and reagent

Ginseng

The ginseng samples were from Tong Ren Tang (Group Lit. Corp in Beijing, China). After being dehydrated, the materials were ground into a powder with a mesh size of 60, sealed, and stored at -20°C until further analysis.

Trafos Cu

Trafos Cu Trade Corp (Av. Lázaro Cárdenas Núm. 2305 Int. G-208 - Col. Las Torres - 44920 Guadalajara, Jalisco, Mexico), Perfect Company (the sole representative in Egypt).

Ethics approved

The Institutional Ethical Committee for Animal Care and Use approved the study's design (code: IACUC-SCI-TU-0213).

Animals and experimental design

The experiment was performed on 60 male albino rats (*Rattus norvigicus*) weighing 130-150 gm and 10-12 weeks of age, procured from NRC in Giza-Egypt and allocated equally to 6 groups (Gp). Gp1 is control group in which rats didn't receive any treatment while Gp2 is Ginseng Gp in which rats treated with ginseng (100 mg/kg/twice a week)

[1]Department of Zoology, Faculty of Science, Tanta University, Tanta, Egypt.
[2]Department of Hormones, Medical Research and Clinical Studies Institute, National Research Centre, Giza, Egypt.

Corresponding Author: Amira Saber Ahmed, Department of Hormones, Medical Research and Clinical Studies Institute, National Research Centre, Giza, Egypt. Email: dr.amira2007@yahoo.com Orcid ID: 0000-0002-3989-1408.

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for 2 weeks. Gp3 is Trafos Cu in which rats orally treated with Trafos Cu (150 mg/kg bw/d) for 4 weeks. Gp4, Co-treated group (Ginseng + Trafos Cu) involved rats that were treated with Ginseng and Trafos Cu for 4 weeks together. Gp5, post-treated group (Trafos Cu + Ginseng), involved rats that were treated with Trafos Cu for 4 weeks and then treated with Ginseng for another 2 weeks. Gp6, self-treated Gp, involved rats that were treated with Trafos Cu for 4 weeks then kept for 2 weeks without treatments.

Blood and serum samples

After the trial was concluded, rats were compassionately euthanized using sodium pentobarbital anesthesia. Blood samples were placed in a glass tube with no additives, allowing for natural clotting, then centrifuged at a speed of 4000 revolutions per minute for 5 minutes. The resulting serum was stored at -18°C until further analysis of the blood parameters could be conducted. Post decapitation, rats were dissected, and the kidney were promptly extracted and halved. Half of kidney samples were fixed in 10% buffer neutral formalin for histology and immunohistochemical processing and the rest was weighed and homogenized for DNA damage, enzymatic and non-enzymatic antioxidant assays.

The assessment of renal function and electrolyte balance

The levels of urea and creatinine in the serum were measured following the method outlined by Patton and Crouch, (1977). To quantify potassium, calcium, sodium and chloride ions, the study conducted by Mutar *et al*., (2020) utilized commercially available Indian Sensa-core electrolyte kits.

Enzymatic and non-enzymatic antioxidant assays

Kidney tissue was weighed and homogenized separately using a Potter Elvenhjem tissue homogenizer. According to Singh *et al*. (2014) and Beutler *et al*. (1963) respectively malondialdehyde (MDA) and reduced glutathione (GSH) concentration were measured in kidney tissue homogenate while Catalase (CAT) were established according to Saggu *et al*. (2014).

Detection of total genomic DNA fragmentation via agarose gel electrophoresis

DNA extraction and fragmentation detection were revealed with salting out extraction method of Elgharabawy *et al*., (2023).

Histological processing

Fresh kidney was fixed in 10% neutral buffered formalin for 24-48 hours by immersion solution, following dehydration, clearing and paraffin embedding, sections and recommended staining them with haematoxylin and eosin (Tousson, 2016).

Immunohistochemical detection for Proliferating cell nucleus antigen (PCNA) and Necrosis Factor Alpha (TNFα)

PCNA and TNFα in kidney tissues were detected using the avidin-biotin complicated techniques of Tousson *et al*. (2011) and Elbandrawy *et al*. (2022), respectively.

Statistical analysis

Data were expressed as means values + SE and statistical analysis was performed using one-way analysis of variance (ANOVA) to assess significant differences among treatment groups. The criterion for statistical significance was set

Table 1: Variations in the kidney functions levels in different groups.

	Creatinine (mg/dl)	Urea (mg/dl)	K^+ (mEq/L)	Na^+ (mEq/L)	Ca^{++} (mEq/L)	Cl^- (mEq/L)
Gp 1 (Control)	0.54$^{\#}$±0.02	37.1$^{\#}$±1.48	3.84$^{\#}$±0.07	135.5$^{\#}$±0.29	1.23$^{\#}$±0.01	100.6$^{\#}$±0.52
Gp 2	0.56$^{\#}$±0.05	36.6$^{\#}$±1.33	3.90$^{\#}$±0.02	135.6$^{\#}$±0.46	1.26$^{\#}$±0.03	100.0$^{\#}$±0.33
Gp 3	0.98*±0.06	50.2*±5.54	5.90*±0.26	144.2*±2.11	1.13*±0.04	111.2*±0.77
Gp 4	0.68$^{\#}$*±0.016	39.8$^{\#}$*±1.36	4.07$^{\#}$±0.034	138.9$^{\#}$*±0.82	1.16$^{\#}$*±0.02	107.1$^{\#}$*±0.39
Gp 5	0.67$^{\#}$*±0.04	36.5$^{\#}$±1.52	4.60$^{\#}$*±0.08	136.8$^{\#}$±0.44	1.20$^{\#}$±0.19	103.0$^{\#}$±0.39
Gp 6	0.84*±0.04	43.2*±1.69	5.59*±0.04	143.8*±2.24	1.12*±0.02	114.9*±0.99

The data is presented in the form of the mean ± standard error, based on ten observations.

*denotes a significant deviation from the control group at $p < 0.01$, while $^{\#}$signifies a significant deviation from the Trafos Cu group at $p<0.01$.

Table 2: Variations in the kidney oxidative stress levels in different groups.

	MDA (nmol/gm tissue)	GSH (mmol/gm tissue)	CAT (mmol/ min/gm/tissue)
Gp 1 (Control)	110.0$^{\#}$±1.362	8.90$^{\#}$±0.125	1195.0$^{\#}$±35.62
Gp 2	91.06$^{\#}$±4.208	10.1$^{\#}$±0.4908	1331.0$^{\#}$±64.15
Gp 3	209.0*±5.683	3.623*±0.628	581.2*±42.77
Gp 4	153.5*$^{\#}$±11.85	6.0*$^{\#}$ ±1.065	932.6*$^{\#}$±65.36
Gp 5	112.3$^{\#}$±4.900	7.843*$^{\#}$±0.412	1012.0$^{\#}$±53.37
Gp 6	184.1*±6.547	4.97*±0.051	806.1*±23.07

The information is shown as the mean ± standard error of ten observations.

*Significant variation from the control group at $p < 0.01$, $^{\#}$Significant variation from the Trafos Cu group at $p<0.01$.

at p<0.01. Analysis was performed using (Graphpad prism, Graphpad software, Inc, La Jolla, CA,USA).

RESULTS AND DISCUSSION

Effects of ginseng on renal functions and electrolyte levels

Table 1 revealed that treated rats with Trafos Cu (Gp3 and Gp6) induced a significant elevation in the levels of urea, creatinine potassium, sodium, chloride and a significant decreased in Ca^{++} levels compared to the control group (Gp1). However, treatment with Trafos Cu with ginseng (as in Gp4 and Gp5) revealed a very promising improvements in these parameters as compared to Trafos Cu (Gp3 and Gp6) with best results for Gp5.

Impact of ginseng on oxidative stress

Table (2) revealed that; treated rats with Trafos Cu (Gp3 and Gp6) induced a significant elevation in peroxidation (MDA) and a substantial decline in concentrations of catalase (CAT) and glutathione (GSH) when compared to the control group (Gp1). Conversely, the administration of ginseng alongside Trafos Cu (Gp4 and Gp5) resulted in a notable reduction in lipid peroxidation (MDA) levels and a significant increase in catalase (CAT) and glutathione (GSH) levels in comparison to Trafos Cu (Gp3 and Gp6), with the most favorable outcomes observed in Gp5.

Table 3: DNA fragmentation in the kidney.

	DNA purity	DNA Conc. (ng/µL)
Gp 1 (Control)	1.9	157.6$^{\#}$±7.08
Gp 2	1.9	139.0$^{\#}$±7.65
Gp 3	1.8	266.7*±10.14
Gp 4	1.9	201.2*$^{\#}$±10.45
Gp 5	1.8	148.5$^{\#}$±8.15
Gp 6	1.9	289.5*±11.33

The data presented in this study is represented as the mean ± standard error (SE) of 10 observations. Notably, significant differences were observed in comparison to the control group (p<0.01) and the Trafos Cu group (p<0.01).

Impact of ginseng in kidney DNA fragmentation

Table 3 and Fig 1 demonstrate a noteworthy decline in DNA damage within the kidneys of rats that received injections of Trafos Cu (Gp3 and Gp6) when compared to the control group (Gp1). Conversely, the introduction of ginseng during the treatment of Trafos Cu (Gp4 and Gp5) led to a significant escalation in kidney DNA damage in comparison to Trafos Cu alone (Gp3 and Gp6), with the most favorable results observed in Gp5.

The influence of ginseng on kidneys structure

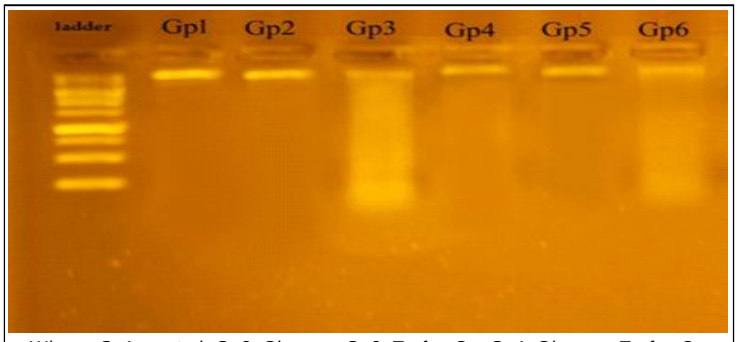
Kidney tissue from the control and ginseng groups revealed that both the cortical and medullary regions had a typical arrangement of glomeruli and renal tubules (Fig 2A and 2B). Conversely, kidney sections in rats injected with Trafos Cu (Gp3 and Gp6) revealed significant contraction in glomeruli and renal tubules, along with impairment of Bowman's capsules, the presence of moderate inflammatory cells, and evident necrosis in tubular cells (Fig 2C and 2F). The glomeruli and renal tubular cells in kidney sections of Gp4 displayed a mild form of atrophy, while, kidney sections in Gp5 showed significant improvement in both the renal tubules and glomeruli, with minimal presence of necrotic tubular cells (Fig 2D and 2E).

Impact of ginseng on PCNA expressions

Fig 3A and 3B demonstrate that kidney sections from both the control and ginseng groups exhibited minimal PCNA expression, however, Fig 3C and 3F revealed a notable increase in PCNA expression in rats injected with Trafos Cu (Gp3 and Gp6). When Trafos Cu was administered alongside ginseng to the injected rats (Gp4 and Gp5), a moderate to mild PCNA response was observed, in contrast to Gp6 (Fig 3D and 3E).

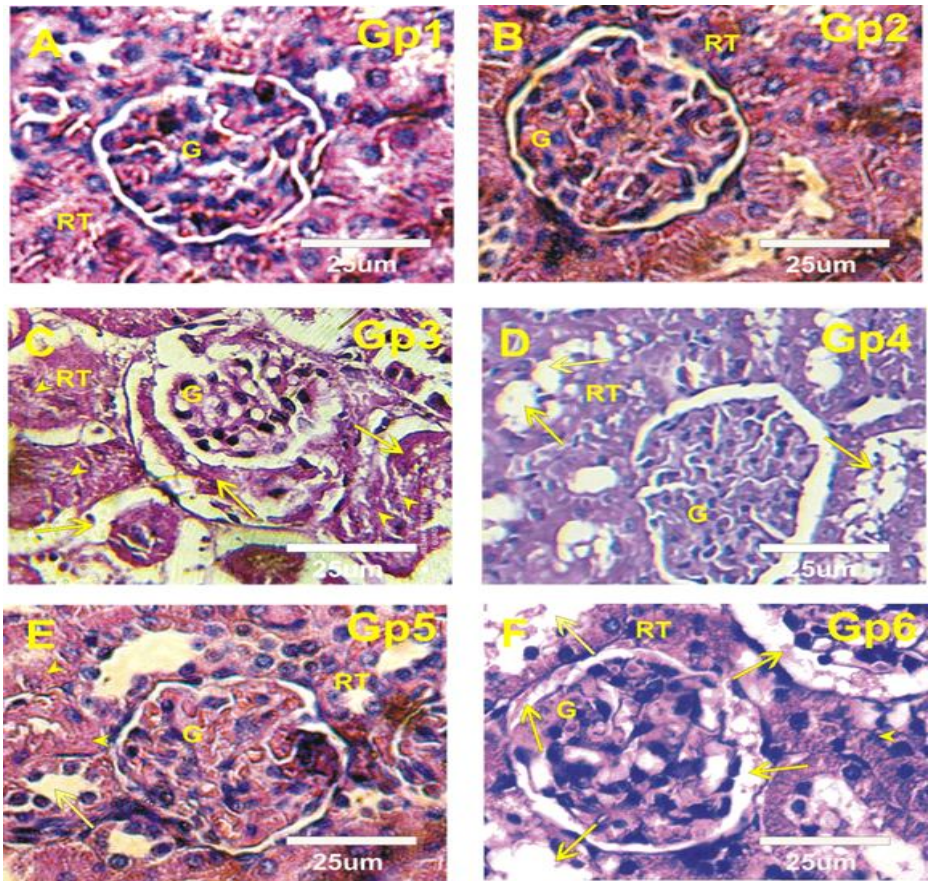
Impact of ginseng on TNFα expressions

Kidney sections in Gp1 and Gp2 revealed negative or weak positive TNFα expressions (Fig 4A and 4B). Conversely, rats that were injected with Trafos Cu (Gp3 and Gp6) displayed a significantly heightened TNFα expression (Fig 4C and 4F).



Where, Gp1: control; Gp2: Ginseng; Gp3: Trafos Cu; Gp4: Ginseng+Trafos Cu; Gp5: Trafos Cu+Ginseng; Gp6: Self-treated Gp.

Fig 1: DNA fragmentation in kidney.



A and B: normal structure glomeruli (G) and renal tubules (RT) in control and ginseng groups, C and F: Significant shrinkage in glomeruli and renal tubules, as well as necrotic tubular cells in treated rats with Trafos Cu (Gp3 and Gp6). D: Mild degeneration was seen in glomeruli and renal tubular cells in kidney sections treated with Ginseng+Trafos Cu. E: Mild necrotic tubular cells (arrowheads) were seen in kidney sections treated with Trafos Cu+Ginseng.

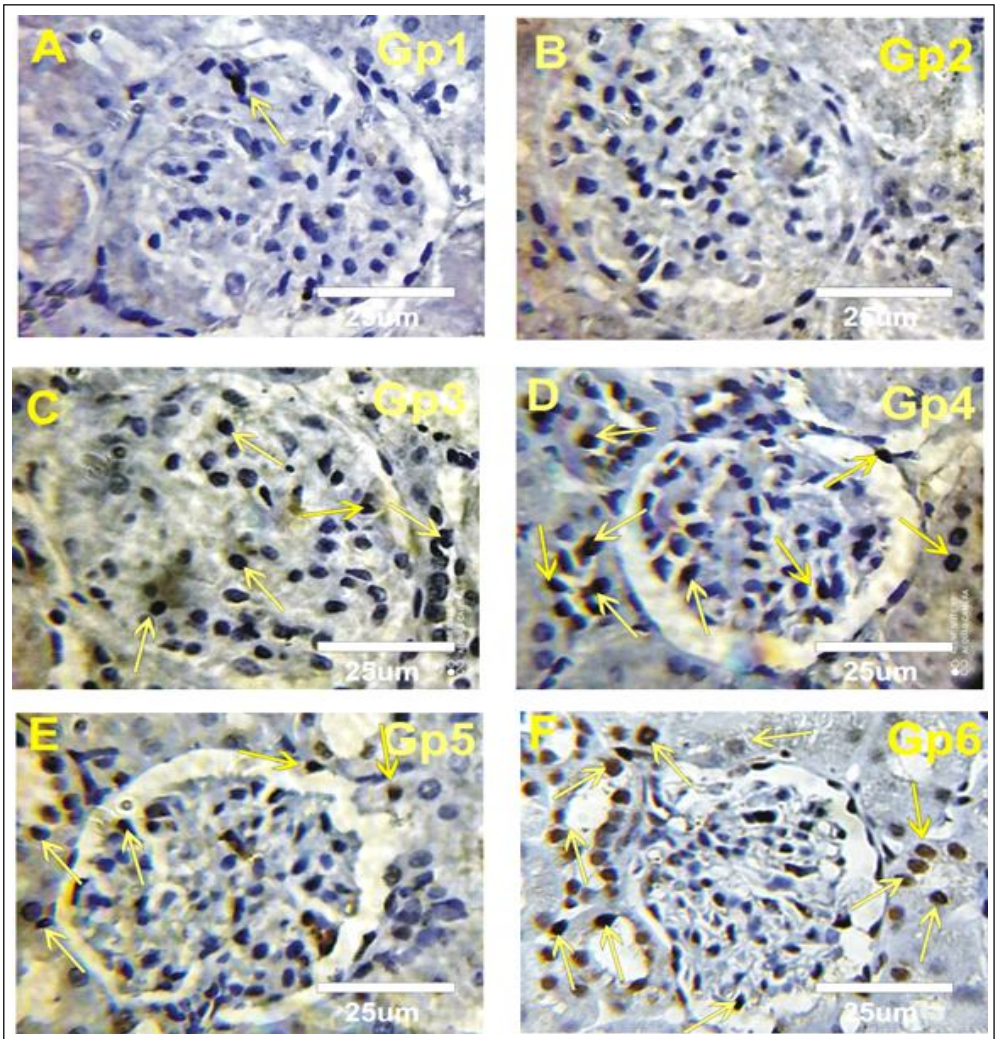
Fig 2: Photomicrographs of kidney sections stained with hematoxylin and eosin.

Conversely, the administration of ginseng alongside Trafos Cu (Gp4 and Gp5) revealed noticeable decrease in TNFα reactions, ranging from moderate to mild, when compared to Gp3 and Gp6 (Fig 4D and 4E).

In modern agriculture, the utilization of PGRs is becoming increasingly significant (Choudhary *et al*., 2023; Wang and Hao 2023). This observation aims to discover ginseng extracts' capacity to lower renal harm precipitated by the management of Trafos Cu in male rats. In the current study, administration of Trafos Cu (Gp3 and Gp6) to rats induced renal toxicity. These findings are in agreement with Tousson *et al*. (2019) who found that; PGR ethophon administered induced renal toxicity in male rats. Our results are consistent with the study of Celik *et al*. (2007) who showed that male rats exposed to plant growth hormones developed liver and kidney injury, leading to comparable outcomes. Our findings are consistent with the study of Soliman *et al*. (2022) who found that; administration of gibberellic acid caused kidney damage and decreased calcium levels.

In contrast, ginseng administration before or after Trafos Cu treatments (Gp4 and Gp5) modulate this results and improved renal toxicity by Trafos Cu in rats. Our results agree with El-Mahalaway *et al*. (2015) and Shahrajabian *et al*. (2019) who reported that ginsenosides modulates kidney functions and structure in treated rats with potassium dichromate.

Current study revealed that; Trafos Cu injection (Gp3 and Gp6) induced elevation in MDA concentration as well as a significant depletion in CAT and GSH concentrations in rat kidney homogenates. Our findings concur with those of Soliman *et al*. (2022) who noted oxidative stress and hepatorenal dysfunction brought on by gibberellic acid. On the other hand, when Trafos Cu was treated with ginseng (Gp4 and Gp5) induced a significant reduction in MDA and elevation in catalase and GSH in rat kidney homogenates. Our findings concur with those of El-Demerdash *et al*., (2021) who found that the aqueous extract of Panax ginseng influences oxidative stress and DNA damage, in treated rats with silicon dioxide nanoparticles. Also our findings



A and B: faint positive reactions in control and ginseng groups. C and F: Strong reaction in injected rats with Trafos Cu (Gp3 and Gp6). D and E: moderate and mild reactions for PCNA in Gp4 and Gp5 respectively.

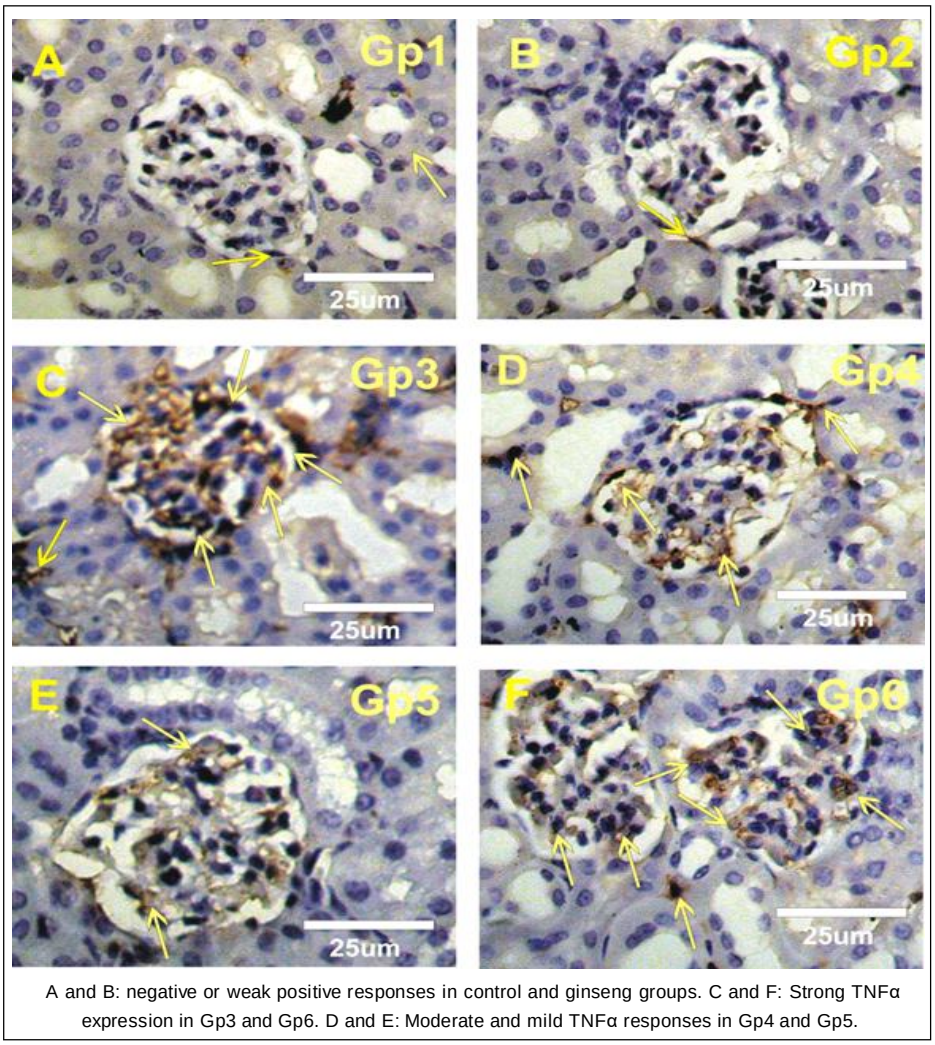
Fig 3: In various groups, kidney sections stained with PCNA.

are consistent with Li *et al*. (2016) and Zhou *et al*. (2022) who reported that Panax ginseng extract modulates renal oxidative stress and apoptosis in treated mice with cisplatin.

Current study revealed that Trafos Cu injection (Gp3 and Gp6) induced elevation DNA damage in kidney rats. These findings are in agreement with Tousson *et al*. (2019) who find that PGR ethophon administered induced renal DNA damage in male rats. In contrast treatments of Trafos Cu with ginseng (Gp4 and Gp5) significantly reduced DNA damage.

Current study revealed that Trafos Cu injection induced renal injury and the treatments of Trafos Cu with ginseng (Gp4 and Gp5) improved kidney structure with best results for post treatments (Gp5). These findings align with previous research conducted by Soliman *et al*. (2022) indicating a correlation between Trafos Cu and liver-related renal damage. These results suggest that Trafos Cu exposure directly impacts the structure and function of the mouse kidney. Our results agree with Kim *et al*. (2014) and Wang *et al*. (2018) who reported that ginsenoside ameliorates acute cisplatin-induced nephropathy.

Ginseng administration reduced renal injury and increased the expression of PCNA and TNFα compared to the Trafos Cu or self-treated groups. Our findings align with the research conducted by Tousson *et al*. (2019), indicating that the administration of ethephon resulted in increased PCNA expression in kidney of rats. Our findings are consistent with El Demerdash *et al*. (2021) who reported that Panax ginseng modulates oxidative stress, DNA damage, apoptosis and inflammations induced by silicon dioxide nanoparticles in rats.



A and B: negative or weak positive responses in control and ginseng groups. C and F: Strong TNFα expression in Gp3 and Gp6. D and E: Moderate and mild TNFα responses in Gp4 and Gp5.

Fig 4: In the photomicrographs of kidney sections stained with TNFα.

CONCLUSION

Trafos Cu induced kidney toxicity, DNA fragmentation, oxidative stress and PCNA, TNF-α expressions alterations. Ginseng has the capacity to mitigate the renal toxicity induced by Trafos Cu in male albino rats.

Conflict of interest

The authors declared no potential conflict of interest with respect to the research, authorship and publication of this article.

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