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Original article

Arsenic-induced ovarian toxicity and the protective efficacy of *Panax ginseng* in mice: a histological and biochemical study

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Abstract

Objective: This study examined the protective effect of *Panax ginseng* against reproductive toxicity caused by arsenic in female NMRI mice.

Materials and methods: Twenty-eight female NMRI mice were divided into four groups for five weeks: a control group, an arsenic-exposed group (5 mg/kg, intraperitoneal), and two treatment groups that received arsenic plus ginseng (200 or 400 mg/kg, oral). After treatment, serum and ovarian tissue samples were collected. Inflammatory markers and oxidative stress parameters were measured, and histological changes were evaluated.

Results: Compared to control group, arsenic exposure reduced primary and secondary follicle counts (both $p<0.05$) and increased atretic follicles ($p<0.001$). Treatment with ginseng improved follicle counts. This effect was more evident in the high-dose group for primary ($p=0.01$) and secondary follicles ($p<0.001$), while both doses showed similar trends in biochemical parameters. Serum Tumor Necrosis Factor Alpha levels significantly increased in the arsenic group compared with control ($p<0.001$). Serum malondialdehyde levels also increased in arsenic group compared to all other groups ($p<0.05$).

Conclusion: Arsenic exposure caused ovarian damage and reduced follicle counts. Ginseng improved ovarian structure and biochemical markers. Both doses showed protective effects, although the high dose had a stronger effect on follicle counts.

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Introduction

Arsenic is a natural metalloid that is widely present in the Earth's crust. It is a toxic element and can enter the human body through different sources, especially contaminated water. Arsenic exposure causes oxidative stress and activates inflammatory responses. These changes are linked to the development of several diseases (Lin et al. 2023). Arsenic exposure

increases the risk of cancer and cardiovascular diseases such as hypertension and atherosclerosis. It also affects the nervous and gastrointestinal systems and impairs reproductive function (World Health Organization 2022). Infertility affects about 10 to 15 percent of couples worldwide, and many cases have no clear cause. Environmental factors such as arsenic exposure may contribute to these cases (Chen et al. 2022; Majdi Seghinsara et al. 2019). Arsenic acts as an endocrine disruptor. It alters hormone levels such as follicle-stimulating hormone and luteinizing hormone. These changes disturb oogenesis and affect female reproductive health. Arsenic exposure reduces oocyte quality and disrupts follicle development. It can also impair ovulation and reduce fertility (Ghasemzadeh et al. 2015; Lin et al. 2023).

Oxidative stress plays a central role in arsenic toxicity. Arsenic increases the production of free radicals (Rouamba et al. 2025). It also binds to thiol groups in proteins and enzymes. This interaction disrupts cellular metabolism, especially in sensitive tissues such as the ovaries (Eslami et al. 2024). These changes increase oxidative stress and inflammation. As a result, ovarian cells are damaged and oogenesis is disturbed (Adeogun et al. 2025).

Panax ginseng (P. ginseng) is a medicinal plant with antioxidant and anti-inflammatory effects (Athari et al. 2023). Its main active compounds are ginsenosides. These compounds protect different tissues by reducing oxidative damage and inflammation (Morshed et al. 2023). Ginseng also affects the pituitary–gonadal axis and helps regulate hormone levels. In female models, it supports oocyte development and reduces cellular damage (Luo et al. 2020; Luo et al. 2021). Studies show that ginseng can reduce inflammatory cytokines such as Tumor Necrosis Factor Alpha (TNF-α) and improve ovarian function (Chei et al. 2020). Evidence suggests that ginseng extracts improve oocyte quality and ovarian function in animal models, indicating its potential benefits for female fertility (Yu et al. 2025).

Exposure to arsenic is increasing globally and is associated with toxic effects on multiple organ systems (Eslami et al. 2024). Oxidative stress and inflammation play a main role in this damage (Adeogun et al. 2025). Several studies have examined the toxic effects of arsenic (Eslami et al. 2024; Ganie et al. 2024). However, few studies have focused on the female reproductive system (Chen et al. 2022). Also, the protective effect of *P. ginseng* on arsenic-induced ovarian toxicity is not well studied. This gap shows the need for more research in this area.

The aim of this study was to evaluate the effect of *P. ginseng* on ovarian damage caused by arsenic in female NMRI mice. We hypothesized that ginseng reduces ovarian injury by decreasing oxidative stress and inflammatory responses, which may help preserve folliculogenesis.

Materials and Methods

Animal population

The Ethics Committee of Yazd University of Medical Sciences approved this experimental study (ethics code: IR.SSU.AEC.1402.028). The study followed the guidelines of the US National Institutes of Health for laboratory animals. Efforts were made to reduce animal suffering. Female mice were kept under controlled conditions with standard light, temperature, and humidity. They had free access to food and water. A total of 28 female NMRI mice (6–8 weeks old, 20–40 g) were randomly divided into four groups (n=7). The control group received normal saline (intraperitoneal). The arsenic group received sodium arsenite (5 mg/kg, intraperitoneal). The low-dose (LDT) and high-dose (HDT) groups received sodium arsenite (5 mg/kg, intraperitoneal) together with *P. ginseng* (200 and 400 mg/kg, oral, respectively). The selected doses were based on previous studies that evaluated

reproductive and oxidative stress outcomes (Li et al. 2002; Zheng et al. 2020). The sample size was selected based on similar experimental studies with comparable endpoints. After five weeks, mice were anesthetized with ketamine (150mg/kg) and xylazine (15mg/kg)(intraperitoneal). Blood samples were collected from the heart. The ovaries were removed. One ovary was fixed in 10% formalin for histology. The other ovary was stored at −80°C for molecular analysis.

Preparation of ginseng

Powdered *P. ginseng* was purchased from Giah Kala Company (Mashhad, Iran). The powder was suspended in distilled water to prepare 1:10 and 1:20 (w/v) suspensions. Each mouse received the *P. ginseng* suspension orally once daily for five weeks.

Histological examination of the ovary

The ovaries were removed and fixed in 10% formalin. The samples were dehydrated with ascending alcohol, cleared with xylene, and embedded in paraffin. Sections (5-6 µm) were stained with Hematoxylin and Eosin (H&E). Follicles (primordial, primary, secondary, and antral) were counted. Histological changes were evaluated using a light microscope.

Gene expression assessment

Total RNA was extracted from ovarian tissue using a commercial kit (ParsTous Biotechnology, Mashhad, Iran) according to the manufacturer's instructions. RNA purity and concentration were measured at 260/280 nm. cDNA was synthesized from 1 µg RNA. Gene expression of *IL-10 (Interleukin-10), TNF-α, Superoxide dismutase (SOD), and Heat shock protein 70 (HSP70)* were measured by real-time PCR. Oligonucleotide sequences of primers are presented in Table 1. Each reaction contained cDNA, primers, SYBR Green, and nuclease-free water (final volume 20 µl). All reactions were performed in triplicate. PCR conditions included initial denaturation at 95°C for 10 min, followed by 40 cycles (95°C for 15 sec, 60°C for 30 sec, and 72°C for 30 sec). Melting curve analysis was performed to confirm specificity. *GAPDH* was used as the reference gene. Relative gene expression was calculated using the 2−ΔΔCt method ().

Table 1. Oligonucleotide primers

Genes	Primer sequence (5'-3')	Product size (bp)
TNF-α	R-CCATAGAACTGATGAGAGGGAG F-GGTGCCTATGTCTCAGCCTCTT	138
IL-10	R-GCCTGGCTCAGCACTGCTAT F-GAAGGCAGTCCGCAGCTCTA	142
SOD	R-CCTTGTGTATTGTCCCCATACTG F-ATGGCGATGAAAGCGGTGT	170
HSP70	R-CCTCGTACACCTGGATCAGCA F-CACCAAGCAGACGCAGACC	71
GAPDH	R-CCAGTGAGCTTCCCGTTCAG F-CACTGCCACCCAGAAGACTG	147

Note: R (Reverse), F (Forward), TNF-α (Tumor necrosis factor-α), IL10 (interlukine-10), SOD (Super oxide dismutase), HSP70 (Heat shock protein 70), and GAPDH (Glyceraldehyde-3-phosphate dehydrogenase)

Measurement of serum levels of TNF-α and IL-10

Serum samples were separated by centrifugation (2500–3000 rpm, 10–15 min). Levels of TNF-α and IL-10 were measured using an ELISA kit (Zellbio, Germany). Samples and standards were added to microplate wells and incubated according to the manufacturer's instructions. After washing, antibodies and Horseradish Peroxidase Avidin D (HRP-avidin) were added. The reaction was completed with substrate solution and stopped with stop solution. Absorbance was measured at 450 nm.

Malondialdehyde (MDA) assay

Malondialdehyde (MDA) levels were measured using a commercial kit (Zellbio,

Germany) based on the thiobarbituric acid (TBA) method. Serum samples were first prepared according to the kit instructions. Briefly, samples were mixed with the reaction reagents and incubated in a boiling water bath for 1 hr to allow formation of the MDA–TBA complex. The samples were then cooled and centrifuged. The supernatant was collected and transferred to a microplate. Absorbance was measured at 535 nm using Microplate spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). MDA levels are reported as nMol/mg protein.

Measurement of Superoxide dismutase (SOD)

Superoxide dismutase (SOD) activity was measured using a commercial kit (Zellbio Co) based on a colorimetric method. Serum samples were prepared according to the kit instructions. Briefly, samples were mixed with the reaction buffer and reagents provided in the kit. Each sample was measured together with its blank. The reaction mixture was incubated at room temperature. Absorbance was measured at 420 nm at two time points (0 and 2 min) using an ELISA reader. SOD activity was calculated according to the manufacturer's instructions and expressed as U/mL.

Statistical analysis

Statistical analysis was conducted using GraphPad Prism version 9 software (San Diego, California, USA). Data normality was tested using the Kolmogorov-Smirnov test. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. A $p < 0.05$ was considered significant.

Results

Ovarian histology and follicle counts

Table 2 and Figure 1 show the ovarian histology data and follicle counts. The corpus luteum count did not differ among the study groups ($p = 0.07$). A significant difference was found in the number of primary follicles among the groups (overall $p < 0.05$). The arsenic group had fewer primary follicles than the control group (0.62 ± 0.96 vs. 6.00 ± 6.31, respectively, $p<0.05$). The HDT group also had a higher primary follicle count than the arsenic group (4.00 ± 4.12 vs. 0.62 ± 0.96, respectively, $p<0.05$). In case of primary follicles count, no significant difference was found between the control group and either treatment group, and no difference was found between LDT and HDT. A significant difference was also found in the number of secondary follicles overall and between Arsenic and HDT groups ($p<0.001$). The arsenic group had fewer secondary follicles than the control group (1.46 ± 2.33 vs. 4.75 ± 2.93, respectively, $p<0.05$). The HDT group had a higher number of secondary follicles than the arsenic group (4.71 ± 2.80 vs. 1.46 ± 2.33, , respectively, $p<0.001$). For the secondary follicle counts, there was no significant difference between the arsenic and LDT groups. Likewise, neither treatment group differed significantly from the control group, and no significant difference was observed between the LDT and HDT groups. The number of Graafian follicles differed among the groups (overall $p<0.001$). All exposed or treated groups had lower Graafian follicle counts than the control group. This difference was significant for the arsenic, LDT, and HDT groups (all $p<0.001$). No significant difference was found among the arsenic, LDT, and HDT groups. Atrophic follicle counts also differed among the groups (overall $p<0.001$). The arsenic group had a higher number of atrophic follicles than the control group (3.23 ± 2.13 vs. 0.083 ± 0.29, respectively, $p<0.001$). Both treatment groups had lower atrophic follicle counts than the arsenic group (LDT: 1.13 ± 1.19, $p<0.05$; and HDT: 1.17 ± 1.16, $p<0.05$). However, both treatment groups still had higher values than the control group (LDT $p<0.05$, and HDT $p<0.05$). No significant difference was found between LDT and HDT in case of atrophic follicles.

Microscopic examination supported these data. The control group showed normal ovarian structure, and follicles at different stages were present. The arsenic group had significantly fewer normal follicles than the control group and significantly more atrophic follicles than the control, LDT, and HDT groups. Both treatment groups showed partial histological improvement. The number of atrophic follicles was lower compared to the arsenic group, and ovarian architecture was better preserved, especially in the HDT group.

Table 2. The mean number of ovarian follicles in the study groups

Variable	Control	Arsenic	LDT	HDT
Corpus luteum	2.75 ± 1.42	1.31 ± 1.38	2.31 ± 1.33	2.38 ± 1.55
Primary follicles	6.00 ± 6.31	0.62 ± 0.96 *	3.16 ± 3.79	4.00 ± 4.12 #
Secondary follicles	4.75 ± 2.93	1.46 ± 2.33 *	3.16 ± 2.27	4.71 ± 2.80 ###
Graafian follicles	1.75 ± 1.22	0.08 ± 0.28 ***	0.16 ± 0.45 ***	0.25 ± 0.53 ***
Atrophic follicles	0.08 ± 0.29	3.23 ± 2.13 ***	1.13 ± 1.19 * #	1.17 ± 1.16 * #

Note: Data are presented as mean ± SD (n = 7 mice per group). Statistical comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. *p<0.05 and ***p<0.001 versus the control group; #p<0.05 and ###p<0.001 versus the arsenic group. LDT, low-dose treatment; HDT, high-dose treatment.

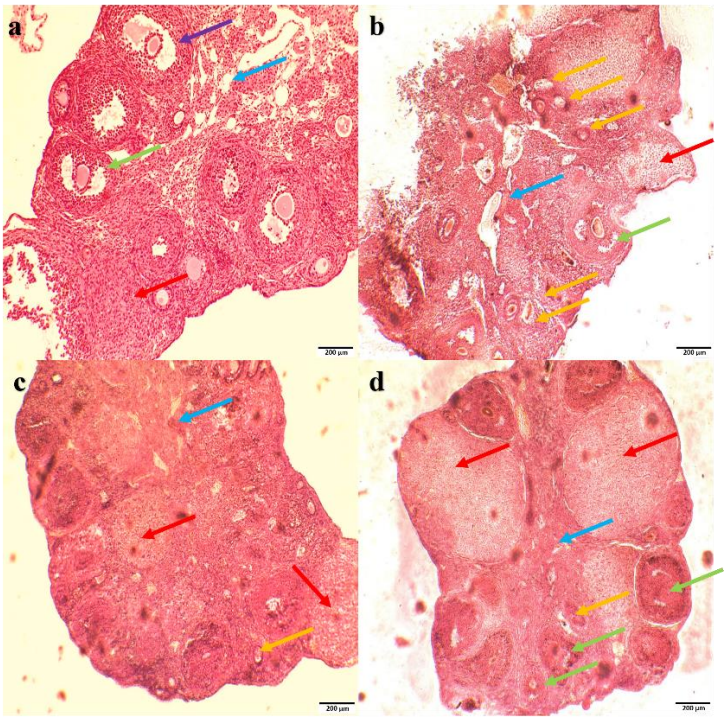

Figure 1. Light microscope analysis of ovarian tissue by hematoxylin and eosin staining. Note: (a) control, (b) arsenic, (c) low dose treatment, (d) high dose treatment. Yellow arrow: atrophic follicle, blue arrow: medulla, red arrow: corpus luteum, green arrow: secondary follicle, purple arrow: graafian follicle. Original magnification ×40. Scale bar = 200μm.

Ovarian gene expression profiles

Figure 2 shows the ovarian gene expression data. No significant difference was found among the groups in *IL-10, TNF-α, SOD, or HSP70* expression. Although the differences were not significant, some patterns were present. *IL-10* expression was the highest in the HDT group. *TNF-α* expression had a higher mean value in the arsenic group than in the other groups. *SOD* expression was higher in both treatment groups than in the control and arsenic groups. *HSP70* expression also had a higher mean value in the HDT group.

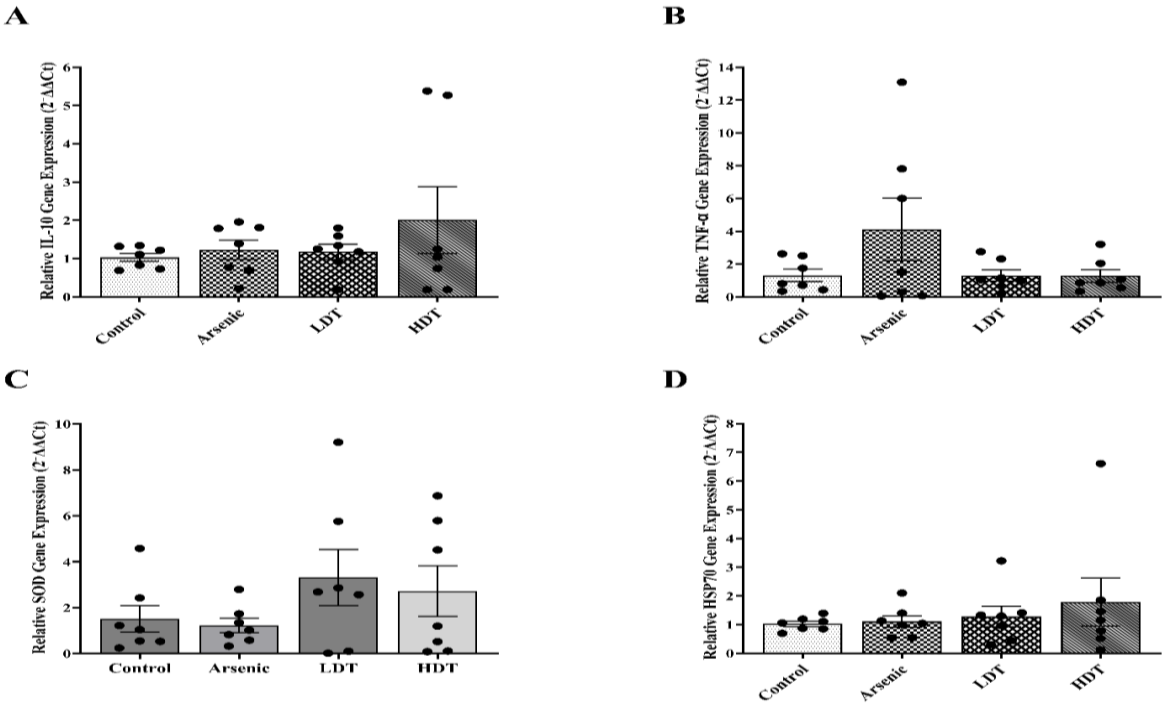

Figure 2. Comparison of gene expression between four groups. Note: Data are presented as Mean ± SEM by using ordinary one-way ANOVA test followed by Tukey's post-hoc test to determine significant differences between each variable in study groups. IL-10: Interleukin 10 (A). TNF-α: tumor necrosis factor-α (B), SOD: super oxide dismutase (C), HSP70: Heat shock protein, (D). LDT (low dose treatment), HDT (high dose treatment).

Serum IL-10 and TNF-α levels

Figure 3 shows the serum cytokine data. Serum IL-10 levels differed between the HDT and arsenic groups. The HDT group had higher IL-10 levels than the arsenic group ($p<0.01$). No other marked pairwise difference is shown in the Figure. Serum TNF-α levels were higher in the arsenic group than in the control group ($p<0.001$). Both treatment groups had lower TNF-α levels than the arsenic group (both $p<0.001$). No significant differences were observed between the LDT and HDT groups in either IL-10 or TNF-α levels.

Oxidative stress markers

Figure 3 also shows the oxidative stress markers. SOD levels were lower in the arsenic group than in the control group ($p<0.001$). SOD levels were also lower in the LDT and HDT groups than in the control group. This difference was significant for both groups. In addition, the HDT group had higher SOD levels than the arsenic group ($p<0.05$). MDA levels were higher in the arsenic group than in the control group ($p<0.001$). Both treatment groups had lower MDA levels than the arsenic group (both $p<0.001$). However, MDA levels in both treatment groups remained higher than in the control group. This difference was significant in both cases.

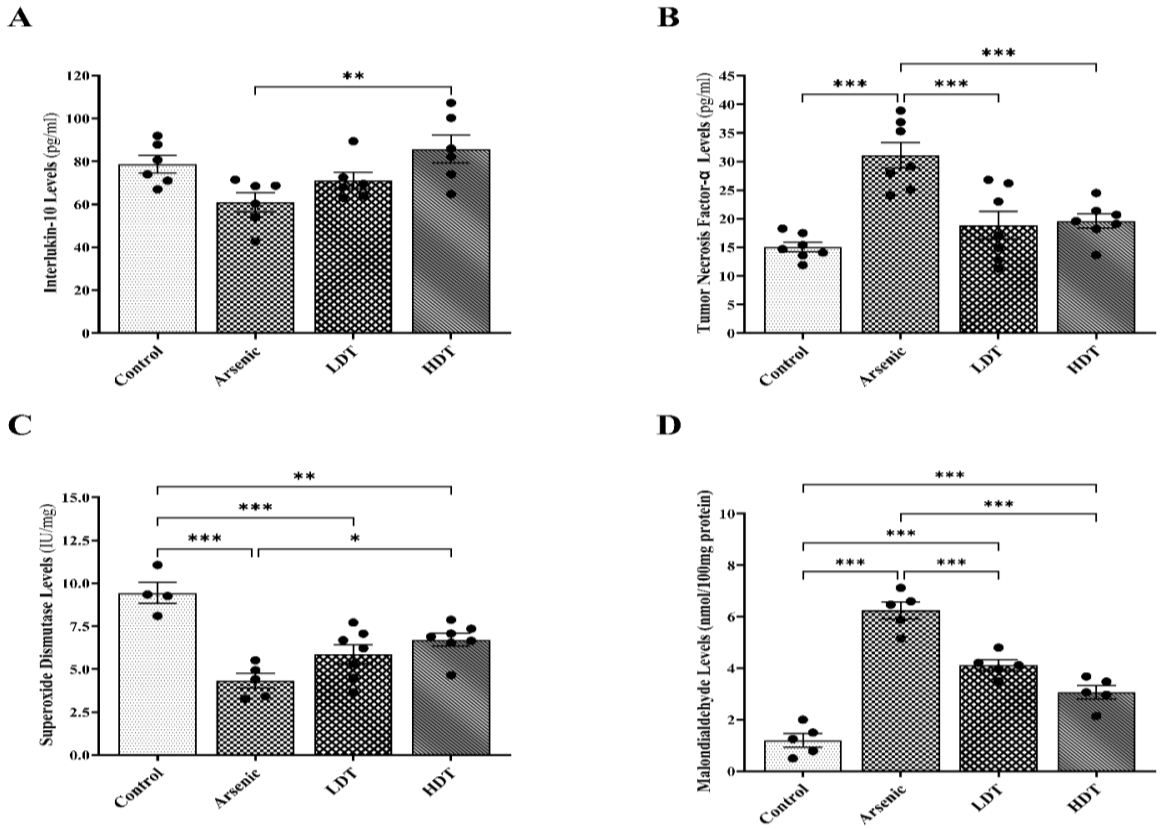

Figure 3. Comparison of levels of TNF-α, IL-10, SOD and MDA between study groups. Note: Data are presented as Mean ± SEM. Statistical analysis was performed by using one way ANOVA test and GraphPad Prism version 9 to compare each variable between study groups. A: Interlukin-10, B: tumor necrosis factor-α, C: super oxide dismutase, D: Malondialdehyde. LDT: low dose treatment, HDT: high dose treatment

Discussion

Arsenic contamination of drinking water is a major global health concern with known links to female infertility (Lin et al. 2023). In general, arsenic and other heavy metals induce oxidative stress, disrupt hormone signaling and follicle development, and promote follicular atresia and inflammation. These effects underlie reported associations between arsenic exposure and ovarian dysfunction as well as decreased ovarian reserve (Zargari et al. 2022). However, most studies have focused on toxic outcomes, with few addressing interventions. Recent animal work shows arsenic upregulates inflammatory signaling (NF-κB) and pro-inflammatory cytokines in the ovary, but it remains unclear whether antioxidants like *P. ginseng* can prevent these changes. In particular, gaps exist in understanding how arsenic perturbs ovarian oxidative/antioxidant balance and cytokine profiles, and whether ginseng anti-oxidant/anti-inflammatory effects can reverse them (Andrade-Feraud et al. 2025; Li et al. 2025). The present study addresses this gap by testing if *P. ginseng* rescues arsenic-induced ovarian oxidative damage and inflammation in mice.

The key findings show that arsenic provoked ovarian oxidative stress and inflammation, while ginseng co-treatment largely normalized these changes. Mechanistically, arsenic likely caused excessive reactive oxygen species (ROS) that overwhelmed antioxidant defenses and triggered NF-κB–mediated inflammation. Consistent with our study, Dash et al (Dash et al. 2020) reported that arsenic intoxication in female mice markedly suppressed antioxidant enzymes (SOD, catalase, and glutathione peroxidase) and up-regulated TNF-α and NF-κB. In parallel, Irnawati et al (Irnawati et al. 2023) found that arsenic significantly increased MDA

and TNF-α while reducing SOD activity in rat uterine tissue. These observations match our data, implying that arsenic-induced ROS and lipid peroxidation drive ovarian damage. Arsenic also boosted pro-inflammatory cytokines. for example, Andrade-Feraud et al (Andrade-Feraud et al. 2025) observed that chronic arsenic exposure in human ovarian cells strongly activated NF-κB and increased secretion of TNF-α and IL-10. Our work similarly found elevated TNF-α in arsenic-only mice, suggesting activation of the same pathways. Clinically, increased ovarian TNF-α and suppressed anti-inflammatory IL-10 would impair follicle survival and hormone balance. *P. ginseng* appears to counteract these processes. In our study, ginseng co-treatment restored antioxidant enzyme activity and reduced MDA, suggesting it scavenged ROS and stabilized ovarian redox balance. This aligns with the known antioxidant action of ginsenosides. Beauty et al (Beauty et al. 2025) likewise reported that ginseng (with exercise) elevated brain Nrf2/HO-1 and IL-10 while lowering pro-inflammatory IL-6 in arsenic-exposed mice. The increase in IL-10 (an anti-inflammatory cytokine) and decrease in IL-6 by ginseng are conceptually consistent with our finding of relative IL-10 preservation in the treated groups. Thus, ginseng antioxidant and anti-inflammatory effects likely underlie the improved follicle counts and reduced markers of oxidative stress we observed. Overall, our results suggest that *P. ginseng* mitigates arsenic-mediated ovarian injury by enhancing antioxidant defenses and shifting cytokine balance towards resolution of inflammation.

Comparing with other recent studies, our findings largely agree with the literature. In the study by Faghani et al (Faghani et al. 2022), which examined nicotine-induced ovarian damage in mice, nicotine reduced healthy follicle counts and antioxidant enzymes (SOD and catalase) and raised MDA, while co-treatment with *P. ginseng* restored hormone levels, increased healthy follicles, and reduced MDA. This pattern mirrors our results: like nicotine, arsenic acted as an ovarian toxin causing oxidative stress and atresia, and ginseng co-treatment counteracted these effects. Similarly, Dash et al (Dash et al. 2020) showed that arsenic-fed female rats had depleted ovarian SOD and elevated TNF-α and NF-κB expression. Dietary N-acetylcysteine (an antioxidant) reversed these changes. Our study extends this by showing *P. ginseng* can play a comparable antioxidant/anti-inflammatory role.

Barakat et al (Barakat et al. 2025) reported that in cadmium-exposed rats, testicular SOD and catalase activities were suppressed and MDA elevated, but *P. ginseng* co-treatment restored these redox parameters. This mirrors our findings in ovaries, highlighting that ginseng's protective antioxidant effect spans different heavy metal toxicities and reproductive tissues.

A limitation of the present study is the relatively small sample size which may have reduced statistical power and limited the generalizability of the findings. Therefore, larger experimental studies are needed to confirm the protective effects of *P. ginseng* against arsenic-induced ovarian toxicity and to validate the observed biochemical and histological changes.

This research indicates that exposure to arsenic adversely affects female reproductive health by reducing follicle counts and harming ovarian tissue. Interestingly, ginseng shows potential as a treatment for arsenic-related reproductive toxicity, as it seems to promote follicle development and improve ovarian function. Both low and high doses of ginseng provided comparable protective effects, suggesting its ability to counteract the damaging impacts of arsenic on the ovaries. The study highlights the need for further research to clarify the mechanisms behind ginseng's effects and to confirm these findings with larger populations.

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Conflicts of interest

The authors had no competing interests.

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Ethical Considerations

This experimental study was approved by the Ethics Committee of Medical Sciences at Yazd University (ethics clearance reference: IR.SSU.AEC.1402.028) and adhered to the guidelines set forth by the US National Institutes of Health for the care and use of laboratory animals

Code of Ethics

IR.SSU.AEC.1402.028

Authors' Contributions

MM and AT carried out the mouse model study. MM, AT, and MA carried out the ELISA assessment and molecular gene analysis. All authors participated in the design and analyses of the studies, wrote, read and approved the final manuscript.

Abbreviations

AS (arsenic), intraperitoneal (IP), low dose treatment (LDT), high dose treatment (HDT), Hematoxylin and Eosin (H&E), Complementary DNA (cDNA), IL-10 (Interleukin 1), TNF-α (Tumor necrosis Factor-a), SOD (superoxide dismutase), and HSP70 (Heat shock protein 70), quantitative real-time polymerase chain reaction (qRT-PCR), GAPDH (Glyceraldehyde 3-phosphate dehydrogenase), malondialdehyde (MDA)

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