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Destructive Effects of Formaldehyde on Mouse Ovaries Ameliorated by *Rosa damascena*

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Abstract

Background: Formaldehyde (FA) is a chemical precursor that has toxic effects on several systems, including the reproductive system. *Rosa damascena* L. (RD) is an ancient herbal drug with various antioxidant substances. In the present study, the effects of RD on mouse ovaries against FA toxicity were investigated.

Methods: In this study, 48 adult female NMRI mice were included and divided randomly into six groups ($n=8$): control, 10% FA group received a single dose of FA (10 mg/kg which was diluted in normal saline) intraperitoneally (i.p), FA+RD10, FA+RD20, and FA+RD40 that received RD extract 10, 20, and 40 mg/kg/d orally, respectively, following FA injection, and RD40 that only received RD extract 40 mg/kg/d orally, without FA administration.

Results: After 40 days of treatment, estrogen and progesterone levels decreased in serum in the FA group relative to the normal group ($P<0.001$). Also, the ovary weight, volume and diameter (WVD), and number of different ovarian follicles were significantly reduced in the FA-treated group ($P<0.05$). Treatment of female mice with doses of 10, 20, and 40 RD improved the harmful effects of FA.

Conclusion: Based on the available evidence in this study, different doses of RD especially its low dose (10 mg/kg) can protect the ovaries against FA toxicity.

Keywords: Formaldehyde toxicity, Female mice, *Rose damascena*, Antioxidant, Ovary

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Introduction

Formaldehyde (FA) is an important chemical precursor widely used in different industries (1). FA adversely affects human health. It is present in steam disinfectants and other disinfectants, cleaning agents, toothpaste, deodorants, cosmetic products, photographs, ink, cartoons, adhesives, and paper (2). In the field of medicine, FA is mainly used for tissue fixation. Also, it is used in treating cystitis and in some materials in dentistry, in hemodialysis solutions, and in some drugs as a protector (3,4).

The findings showed that FA has poisonous effects on the cardiovascular, skin, respiratory, nervous, urinary, and other systems (5,6). One of the important poisonous effects of FA is on the reproductive organs (7,8). In the female experimental models, FA causes infertility (9), hypoplasia in the ovary (10), decreased number and size of mature follicles (by inducing oxidative stress and *apoptosis)* (11,12), smaller oocytes, fewer mitochondria, fibrosis, irregular estrous cycles, and decreased reproductive hormones (12-14). The main mechanism of FA toxicity is through increased reactive oxygen species (ROS), apoptosis, increased oxidative stress of the ovary, decreased levels of antioxidants, and disrupted cellular functions (11,15).

Rosa damascena L. (RD) is an ancient herbal drug known as "Gole Mohammadi" in Iran (16). Various antioxidant substances and components including terpenes, glycosides, flavonoids, anthocyanins, fatty oil,

and inorganic acids have been isolated from RD (17-19). The antioxidant properties of RD have been confirmed by researchers in various disease models (18), such as cardiovascular disease (20), diabetes mellitus (21), Alzheimer's disease (22), and testicular damage (23). Therefore, in this study, the defensive properties of the aqueous extract of RD flowers against toxicity by FA in the ovaries of female rats were investigated.

Methods

Preparation of aqueous extract

Rosa damascena petals were procured from Kashan, Iran, and were approved by the Herbal Medication Research Center in Kerman, Iran. A sample (code: KF1362) was preserved in the herbarium of the School of Pharmacy, Kerman, Iran. The plant flowers were washed, dried, and powdered. To prepare the aqueous extract, 60 g of raw powder was added to deionized water 250 mL and kept at 4 °C for 48 hours. Then, the extract was passed through a filter, dried by rotary evaporation at 50 °C, and concentrated by a freeze dryer to get the solid extract (yield: 20% relative to dry plant). Finally, various doses of RD were obtained and stored at 4 °C (24).

Animals and treatments

Forty-eight adult NMRI female mice weighing 25–30 g were acquired from Kerman University of Medical Sciences. The mice had free access to food and water and were kept in standard condition, 12-hour light/dark cycle and a temperature of 25°C. They were divided randomly into 6 groups ($n=8$). The control group received saline (10 mL/kg), 10% FA group received a single dose of FA (10 mg/kg that was diluted in normal saline) intraperitoneally (i.p). The RD40 group only received RD extract 40 mg/kg/daily orally, FA + RD10, 20, and 40 groups received RD extract 10, 20, and 40 mg/kg orally, respectively for 40 days following FA administration (24).

Assay of hormone concentrations

The female mice were anesthetized by ether inhalation on day 41 of the experiment until the mice had no response to a needle stimulus (24,25). Some blood samples were taken from the mouse's heart and centrifuged at 4000 g for 5 minutes. The separated serums were kept at -20°C. Estrogen and progesterone were analyzed using kit instructions (ELISA Kit, USA; FAX, Webster, TX).

Ovary histological assessment

After the animals were sacrificed, the ovaries were removed and defatted and their weight, volume, and diameter (WVD) were measured. They were fixed in FA (10%), then, they were embedded in paraffin. Five-µm-thick sections were made, and then, stained using hematoxylin and eosin (H&E). To evaluate histological changes of follicles in the ovarian parenchyma (the number of primary, antral, secondary, and atretic follicles and corpus luteum) 10–14 microscopic fields of each ovary were examined (26).

Statistical analysis

The data were analyzed using SPSS version 20 and reported as mean ± SEM. Shapiro-Wilk test was performed to check the normality, and one-way analysis of variance (ANOVA) was used to compare the groups, followed by Tukey's post-hoc test. The Kruskal-Wallis test was used to analyze the non-parametric results. P-values less than 0.05 were considered statistically significant.

Results

Hormone assays

Figures 1A and 1B show the estrogen and progesterone levels in the serum of the studied groups. The levels of estrogen and progesterone in serum decreased significantly in the FA group compared to the control group ($P<0.001$). RD extract (doses of 10, 20, and 40) significantly increased levels of estrogen and progesterone compared to the FA group ($P<0.001$). There were no significant differences between the different doses of RD.

Volume, diameter, and weight of ovary

Table 1 shows the results of comparing the ovary WVD between different experimental groups. Ovary WVD in the FA group decreased significantly compared to the control and RD40 groups ($P<0.001$). RD extract significantly improved ovary WVD compared to the FA group ($P<0.05$). Different doses of RD did not affect ovary WVD.

Histological changes of follicles in the ovarian parenchyma

The normal schematic construction of the ovary can be seen in images A (control) and B (RD40) in Figure 2. FA changed the parenchymal structure and reduced the number of primary, antral, secondary, and atretic follicles and corpus lutea in the ovary compared with the control and RD40 groups (Figure 2C, $P<0.001$). Treatment with various doses of RD (FA + RD10, FA + RD20, and FA + RD40) ameliorated these changes relative to the FA group ($P<0.05$) (Figure 2D-F and Table 2).

Discussion

This study examined the effect of FA and RD in three areas: morphology, hormone production, and follicle condition. The results showed that ovarian parameters, including the WVD, primary, secondary, atretic, and antral follicles, corpora lutea, and the hormone profile, changed following the administration of FA versus controls. Oral administration of RD relatively restored these effects. Previous studies have also shown significant changes in ovarian parameters with FA administration (10,11),

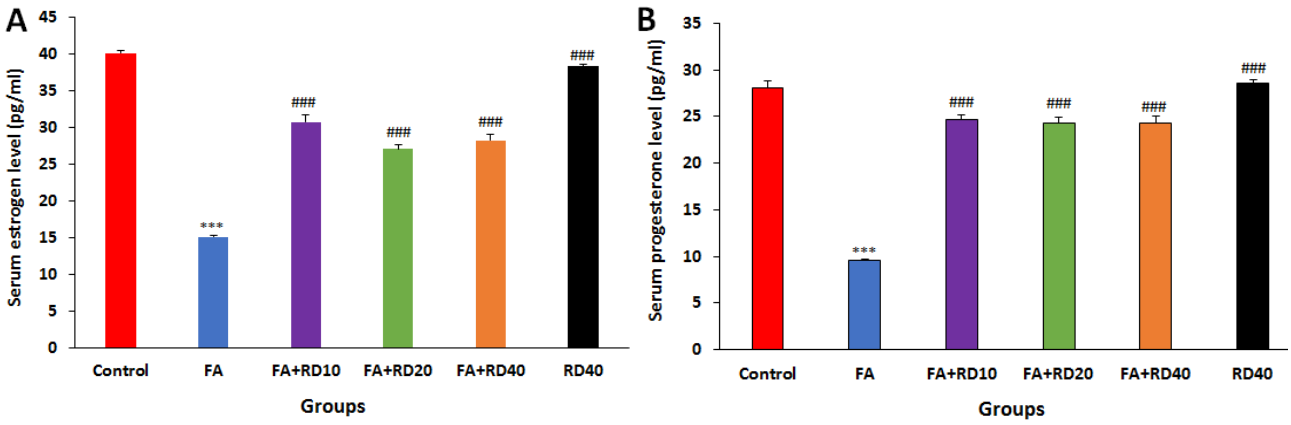

Figure 1. The serum concentration of estrogen and progesterone in the experimental groups. *** $P<0.001$ Significant differences compared to the control group. ### $P<0.001$ Significant differences compared to the FA group. Data are expressed as mean ± SEM. FA: formaldehyde; RD: *Rosa damascena*

Table 1. Comparison of the ovary weight, volume, and diameter among different groups (mean ± SEM, n = 8)

Group/parameters	Weight (mg)	Volume (mm^3)	Diameter (mm)
Control	9.6 ± 0.26	9.2 ± 0.2	3.9 ± 0.05
FA	8.4 ± 0.2***	8.1 ± 0.1***	3 ± 0.04***
FA + RD10	8.8 ± 0.1##	8.5 ± 0.1##	3.2 ± 0.06###
FA + RD20	8.9 ± 0.1##	8.6 ± 0.1#	3.3 ± 0.07###
FA + RD40	8.9 ± 0.1##	8.6 ± 0.2##	3.1 ± 0.09###
RD40	9.7 ± 0.3###	9.3 ± 0.3###	3.9 ± 0.07###

* Significant differences vs. control group (*** $P<0.001$). # Significant differences vs. FA group (# $P<0.05$, ## $P<0.01$, ### $P<0.001$). Data are stated as mean ± SEM. FA: Formaldehyde; RD: *Rosa damascena*.

as observed in the present study with intraperitoneal administration of 10 mg/kg FA. The findings of the studies also showed that FA administration leads to ovarian histopathology by adversely affecting structures and hormones through apoptosis, ROS production, reduced ovarian antioxidant enzyme SOD, and increased malondialdehyde (MDA) and lipid peroxidation (12,15,27). The ROS produced in the ovary leads to apoptosis of granulosa cells and changes in ovarian blood flow (7,28,29). FA could decrease reproductive hormones, damage ovarian histopathological structure, and damage genetic materials in the oocyte (12). Wu et al reported that FA reduced viability and increased apoptosis and oxidative stress in the HL-1 cardiac muscle cell line through changes in SOD, glutathione (GSH), MDA, and caspase-3 in both pregnant mice and their offspring (30). Kareem et al reported that FA significantly decreases estrogen and progesterone levels in female mice (14). Also, using this solvent leads to damage to the ovaries by disruption in the function of the endocrine glands and changes in their histological structure, decreasing estrogen and progesterone production in the ovaries (14). Our findings confirmed that FA administration reduced estrogen and progesterone in female mice.

The follicle is the fundamental functional component of the ovary. It contains an immature oocyte surrounded by several layers of specialized follicular cells and theca cells (31). According to the results, the number of primary follicles, secondary follicles, and corpora lutea were reduced significantly in the FA group vs. the control and RD40 groups. It is hypothesized that FA affects ovarian follicles, leading to a disruption in ovum maturation and delaying ovulation, and may lead to menstrual problems in females who are exposed to FA at work (7,14,32,33). FA can engage with molecules on cellular membranes and disrupt cellular functions, which leads to apoptosis and cell death.

The oxidation of FA leads to the production of formic acid and CO_2, which can reduce the activity of antioxidant enzymes and increase lipid peroxidation, causing oxidative stress in the ovaries (11,34,35). Therefore, the changes in the ovaries of mice in this study may be due to FA-induced oxidative damage and RD due to its scavenging properties, it can eliminate free radicals and increase antioxidant defense (36).

However, RD treatment had antioxidant effects on neurons related to learning and memory (37) and various disorders, such as testicular damage (24), acetaminophen-induced oxidative stress (38), and diabetes (39). Phytochemical tests have revealed the presence of tannins, carbohydrates, phenols, flavonoids, sterols, alkaloids, and saponins in RD. Phenolic acids, flavonoids, and phenols are abundantly found in RD (40,41). Quercetin and gallic acid are the most crucial phenolic compounds of RD with antioxidant properties (42). Previous studies reported that oxidative disorders in the ovary are improved by antioxidant therapy (43,44). In the present study, the beneficial effects of RD are probably due to its antioxidant properties. However, more research is needed to prove the effects of RD.

Conclusion

In summary, the present study showed that IP injection of 10 mg/kg FA led to adverse changes in the number of ovarian follicles, ovarian parameters, morphology, and

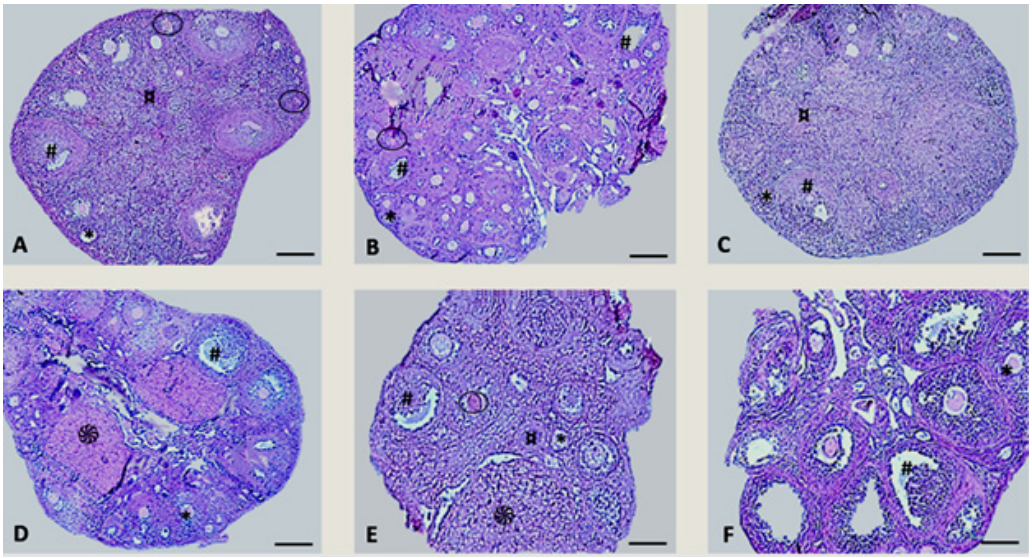

Figure 2. Histological sections of ovary. The normal structural sections of the ovary are shown in the control (A) and RD40 (B) groups. The histological changes in the FA-treated group (C) show that there is a decrease in the number of primary (o), secondary (*), antral (#), and atretic follicles (▫) and corpora lutea (֍) so that reversed in FA + RD10 (D), FA + RD20 (E), and FA + RD40 (F) groups. Hematoxylin and eosin staining. Scale bar = 100 µm

Table 2. The number of primary, secondary, antral, atretic follicles, and corpus luteum per section of ovary mice (mean ± SEM, n = 8)

Group/parameters	Primary follicle	Secondary follicle	Antral follicle	Atretic follicle	Corpus luteum
Control	9.8 ± 0.2	11.6 ± 0.1	9.3 ± 0.2	1.5 ± 0.2	2.1 ± 0.03
FA	8.1 ± 0.1***	9.2 ± 0.2***	8.1 ± 0.09***	0.4 ± 0.1***	1 ± 0.05***
FA + RD10	8.5 ± 0.2***	9.4 ± 0.2***	8.4 ± 0.1***	0.7 ± 0.08**	1 ± 0.03***
FA + RD20	8.7 ± 0.5***#	9.8 ± 0.2 ***	8.7 ± 0.1**#	1 ± 0.02*#	1 ± 0.03***
FA + RD40	8.9 ± 0.1**#	9.9 ± 0.3***	8.8 ± 0.1**##	1 ± 0.03*#	1.1 ± 0.06***
RD40	9.8 ± 0.3###	11.9 ± 0.3###	9.4 ± 0.1###	1.3 ± 0.2###	1.9 ± 0.1###

* Significant differences vs. control group (*P<0.05, **P<0.01, ***P<0.001). # Significant differences vs. FA group (#P<0.05, ##P<0.01, ###P<0.001). Data are expressed as mean ± SEM. FA: Formaldehyde; RD: *Rosa damascena*.

hormone profiling. These findings indicate that due to the antioxidant properties of RD, treatment with different doses of RD especially its low dose (10 mg/kg) effectively protected the ovaries against FA-induced damage.

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Competing Interests
The authors declare no conflict of interests.

Ethical Aproval
The protocol was approved by the Ethics Committee of Bam University of Medical Sciences (Ethical code: IR.MUBAM.REC.1401.043).

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