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Protective Effect of Tyrosol on Cisplatin–Induced Ovarian Inflammation and Oxidative Stress in Rats

Efecto protector del tirosol sobre la inflamación ovárica y el estrés oxidativo inducidos por cisplatino en ratas

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ABSTRACT

Ovarian cancer is a widespread type of cancer among gynecologic cancers and has a very high mortality rate. For this reason, the search for new treatments continues. Tyrosol is a phenolic compound with antioxidant and anti–inflammatory activity. The study, it was investigated the effect of Tyrosol on oxidative stress and inflammatory parameters in cisplatin–induced ovarian inflammation and oxidative stress in rats. For this purpose, twenty–four female Wistar albino rats were divided into four groups: control, Cisplatin, Tyrosol, and Cisplatin+Tyrosol. Cisplatin was administered intraperitoneally at 6 mg·kg^{-1} twice, once a week. Tyrosol (20 mg·kg^{-1}) was administered daily by oral gavage for fourteen d. Oxidative stress and inflammatory biomarkers were measured in ovarian tissue. Cisplatin administration increased Malondialdehyde (MDA), tumor necrosis factor alpha (TNF–α), interleukin 6 (IL–6), and interleukin 1 beta (IL–1β) levels in the ovaries, while Glutathione (GSH), Glutathione Peroxidase (GSH–Px), and Catalase levels were decreased. Tyrosol administration was shown to decrease oxidative stress parameters and inflammatory cytokines. In conclusion, it can be say that the protective activity of Tyrosol against Cisplatin–Induced ovarian inflammation and oxidative stress is realised through antioxidant and anti–inflammatory mechanisms.

Key words: Ovarian; cisplatin; tyrosol; protective effect; rat

RESUMEN

El cáncer de ovario es un tipo de cáncer muy extendido entre los cánceres ginecológicos y tiene una tasa de mortalidad muy alta. Por este motivo, continúa la búsqueda de nuevos tratamientos. El Tirosol es un compuesto fenólico con actividad antioxidante y antiinflamatoria. En el estudio, investigamos el efecto del tirosol sobre el estrés oxidativo y los parámetros inflamatorios en la inflamación ovárica y el estrés oxidativo inducidos por cisplatino en ratas. Para ello, veinticuatro ratas albinas Wistar se dividieron en cuatro grupos: control, Cisplatino, Tirosol y Cisplatino+Ttirosol. El Cisplatino se administró por vía intraperitoneal a 6 mg·kg^{-1} dos veces, una vez por semana. Se administró Tirosol (20 mg·kg^{-1}) diariamente mediante sonda oral durante catorce d. Se midieron el estrés oxidativo y los biomarcadores inflamatorios en el tejido ovárico. La administración de Cisplatino aumentó los niveles de Malondialdehído (MDA), factor de necrosis tumoral alfa (TNF–α), interleucina 6 (IL–6) e interleucina 1 beta (IL–1β) en los ovarios, mientras que, el glutatión (GSH), la glutatión peroxidasa (GSH–Px), y los niveles de catalasa disminuyeron. Se demostró que la administración de tirosol disminuye los parámetros de estrés oxidativo y las citocinas inflamatorias. En conclusión, podemos decir que la actividad protectora del tirosol contra la inflamación ovárica y el estrés oxidativo inducidos por cisplatino se realiza a través de mecanismos antioxidantes y antiinflamatorios.

Palabras clave: Ovario; cisplatino; tirosol; efecto protector; rata

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INTRODUCTION

Cancer is the second leading cause of death globally and a common cause of death in both developed and developing countries [1]. Ovarian cancer is the second most common gynecological tumor in women in the United States and the fifth most common cause of cancer-related death in women [2]. Therefore, research aimed at increasing the effectiveness of ovarian cancer treatment and reducing the side effects of chemotherapeutic drugs remains critical [1, 2].

The treatment of ovarian cancer primarily favors Cisplatin, one of the most widely used anticancer drugs worldwide [3]. While the multifaceted mechanism of Cisplatin's anticancer effect and its ability to damage the DNA of cancer cells are significant advantages, its toxicity to organs such as the kidneys, heart, and liver is a severe disadvantage [4]. In addition, ovarian cancer patients treated with Cisplatin often develop resistance to the drug, experience changes in the cellular import and export processes of the drug, and suffer severe toxic effects, ranging from alterations in DNA damage repair mechanisms in healthy cells to disruptions in apoptosis and autophagy [4, 5]. Cisplatin binds to DNA rings and blocks them, causing DNA damage [5]. It also causes reproductive abnormalities such as early ovarian failure, primordial follicle toxicity, oocyte death, a decrease in hormones such as anti-Müllerian hormone (AMH) and inhibin, and endocrine malfunction [6]. Considering that Cisplatin is a very effective chemotherapeutic drug despite all these disadvantages, the search for combined therapies to reduce the toxic effects of Cisplatin has come to the forefront [7, 8].

Cancer patients employ a number of complementary and alternative medicine methods to deal with the problems and difficulties of cancer, which can have an impact on their quality of life [1] For instance, Ayazoglu *et al.* [9] reported that *Gallic acid*, a phenolic compound, demonstrated an antioxidant protective effect in ovaries against Cisplatin-induced ovarian damage. Many studies have emphasised the antioxidant and anticancer properties of Tyrosol, one of the natural phenolic compounds found in extra virgin Olive oil [10, 11, 12]. In a study of 2,411 healthy Italian women over 45 years of age and 1,031 Italian women with ovarian cancer, it was found that ovarian cancer rates were lower in Italy compared to other European countries and that this was associated with Olive oil consumption in the diet [13].

This study aimed to reveal the possible protective effects of Tyrosol on ovarian inflammatory status and the oxidative stress caused by Cisplatin.

MATERIAL AND METHODS

Ethics

The study received ethical approval from the Local Ethics Committee for Experimental Animals at Hatay Mustafa Kemal University (Decision No. 2023/01-08, Hatay, Turkey). The animals and the experimental studies were provided and conducted by the Hatay Mustafa Kemal University Experimental Research Centre

Study design

Wistar albino female rats (*Rattus norvegicus*) (6-8 weeks and 250-300 g) were used in the study. Animals were housed in standard plastic cages with a 12-hour light/dark cycle, in an environment controlled at 20-22°C and regulated humidity. Unrestricted access to food and water was provided throughout the study. Rats were randomly and equally divided into groups using a random number generator to ensure unbiased allocation. Animal care and experimental protocols adhered strictly to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. The rats were divided into four groups equally: control (C), Cisplatin (CP), Tyrosol (Tyr), and Cisplatin+Tyrosol (CP+Tyr) groups (n= 24, per 6). Cisplatin (6 $mg{\cdot}kg^{-1}$) (Cisplatin Kocak 25 $mg{\cdot}50\ ml^{-1}$) once a week, for a total of two administrations [14]. Tyrosol (Sigma Aldrich, %98) was administered in saline and administered by oral gavage at a dose of 20 $mg{\cdot}kg^{-1}$ daily for 14 days -d- [14]. The control group was administered 1 ml of solvent orally, the same gavage volume as that given to the other groups.

At the end of the study, animals were sacrificed under anesthesia with xylazine (10 $mg{\cdot}kg^{-1}$) (Rompun, 20 $mg{\cdot}ml^{-1}$) and ketamine (100 $mg{\cdot}kg^{-1}$) (Ketalar, 100 $mg{\cdot}ml^{-1}$). Euthanasia was confirmed by monitoring respiration and heart rate. Ovarian tissues were collected and stored at -20°C until analysis. All analyses were performed on the obtained ovarian tissue. To evaluate the effects of Tyrosol, ovarian weight was measured, along with oxidative stress parameters (malondialdehyde (MDA), glutathione (GSH), glutathione peroxidase (GSH-Px), and catalase) and inflammatory cytokines (TNF-α, IL-6, and IL-1β).

Ovarian weight

The right and left ovary samples were thoroughly cleaned, weighed on a precision balance (Daihan, SC210, Turkey), and the averages were used to express the ovarian weight in milligrammes.

Ovarian oxidative stress (MDA, GSH, GSH-Px, and Catalase) analysis

The two ovaries (left and right) were collected and thoroughly homogenized using Tris-buffered saline (pH 7.4). The homogenate was then centrifuged (Nuve, Nf 800R, Turkey) 3220 G for 60 min and supernatant was seperated and the levels of malondialdehyde (MDA), glutathione (GSH), glutathione peroxidase (GSH-Px), and catalase (CAT) were measured using a spectrometer (Shimadzu, UV-1700, Japan), as described in the studies by Arkali *et al.* [16]. The levels of MDA and GSH were measured in nmol per gram of tissue, whereas the amounts of GSH-Px and catalase were measured in IU per gram of protein and ku per gram of protein, respectively.

Ovarian inflammatory cytokine (TNF-α, IL-6, and IL-1β) analysis

The right and left ovarian tissues from each sample were mixed and homogenized using phosphate-buffered saline (PBS) (pH 7.4) at a concentration of 1/10 (w/v), following the guidelines provided by the test kits. The resulting homogenate was subjected to centrifugation (Nüve, Nf 800R, Turkey) with a force of 10000 G for a duration of 5 min at a temperature of +4°C. The supernatant, was gathered and utilized for analysis. The amounts of tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β) were were measured on tissue serum samples with commercial ELISA kits (Bostonchem), and microplate reader (Erba Manheim, Lisascan EM, Czech Republic) and expressed in picograms per milliliter ($pg{\cdot}mL^{-1}$).

Statistical analysis

The study evaluated the data statistically. For all variables obtained, parametric test assumptions were applied before proceeding to significance tests. The variables were analyzed by the Shapiro-Wilk test for normality and Levene's test for homogeneity. Then, one-way analysis of variance (ANOVA) was used to control the difference between variables statistically. For the variables in which the difference between the groups was significant, the Tukey test was used as a post-hoc test.

All statistical analyses were analyzed with a minimum 5% margin of error. The IBM SPSS software was used for all statistical analyses, and all results were expressed as mean ± standard error of the mean (SEM)

RESULT AND DISCUSSION

Ovary weights

The mean ovarian weights of the C, CP, Tyr, and CP+Tyr groups were 34.17 ± 1.11, 28 ± 1.39, 30.67 ± 1.87, and 35 ± 1.84 mg, respectively (FIG. 1). Statistically analyzed, it was observed that there was no difference between the control group and the other groups. However, the CP and CP+Tyr groups were different (*P*=0.019).

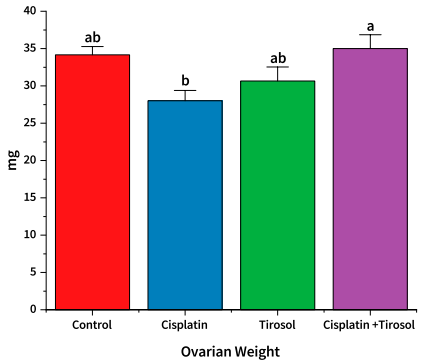

FIGURE 1. Ovarian weights (mg). Values are mean ± SEM, and letters (a, b, and ab) on the columns indicate statistical differences between groups

There are numerous studies investigating the effects of cisplatin treatment on ovarian weights [17, 18, 19]. A study conducted on rats demonstrated that various doses and durations of cisplatin administration significantly reduced both body weight and ovarian weights [17]. Similarly, another study observed that administering cisplatin at a dose of 6 mg·kg^{-1} once a week resulted in reduced ovarian weights [18]. Additionally, a study proved that the weights of ovaries exposed to 2 mg·kg^{-1} cisplatin for ten days significantly declined in C57 albino mice [19]. A further study reported that cisplatin reduces ovarian weights, increases oxidative stress, and significantly decreases ovarian reserves [20]. In this study, consistent with previous studies, cisplatin administration caused a reduction in ovarian weights in rats; however, tyrosol treatment did not result in a statistically significant increase in ovarian weights.

Ovarian MDA, GSH, GSH–Px, and Catalase Levels

The CP group had the highest MDA levels, with a mean of 19.13 ± 1.41. In comparison, the C, Tyr, and CP+Tyr groups had mean MDA levels of 11.96 ± 1.36, 12.46 ± 0.69, and 13.48 ± 1.33, respectively (FIG. 2). The difference between the CP group and the other groups was statistically significant (*P*=0.002).

The GSH levels of the groups were measured as 6.04 ± 0.11 in the C group, 5.71 ± 0.19 in the CP group, 6.70 ± 0.20 in the Tyr group, and 6.24 ± 0.12 in the CP+Tyr group. While the difference between the CP group and the C and Tyr groups was significant, no significant difference was found between the CP and CP+Tyr groups (*P*=0.003).

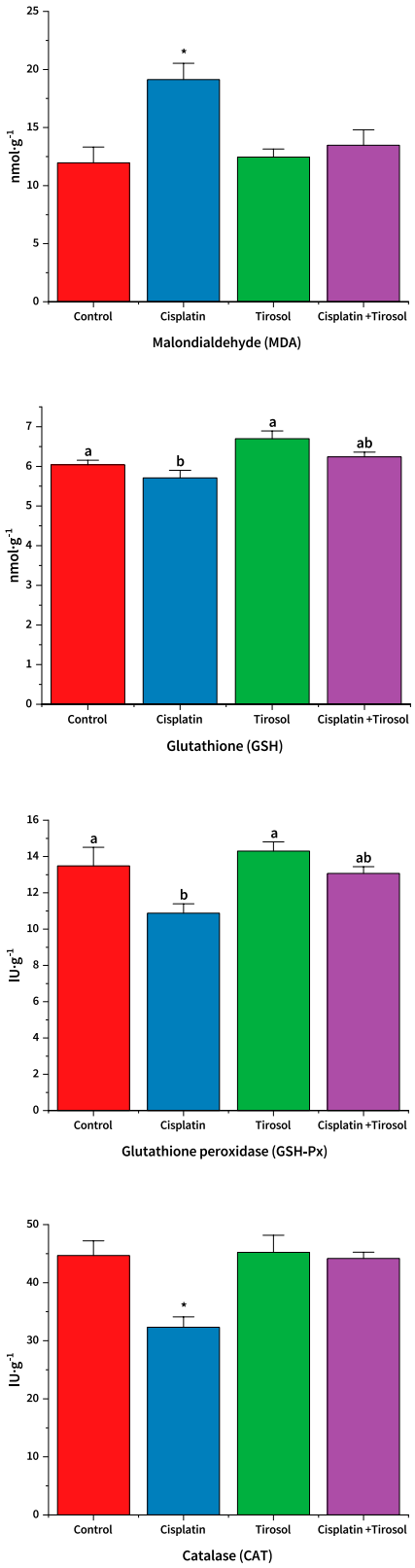

FIGURE 2. MDA, GSH, GSH–Px and Catalase levels in ovarian tissue. MDA, **P*=0.002. GSH, *P*=0.003. GSH–Px, *P*=0.010. Catalase, **P*=0.001. Letters on columns (a, b and ab) indicate statistical difference

GSH-Px levels of the study groups (C, CP+Tyr, CP+Tyr) were measured as 13.48 ± 1.03, 10.88 ± 0.51, 14.30 ±0.50, and 13.06 ± 0.38, respectively (*P*=0.010). The CP group had the lowest GSH-Px levels, which significantly differed from the C and Tyr groups, in line with the GSH findings. The Tyr and CP+Tyr groups were similar to the control group (*P*=0.010).

Catalase levels of the C, CP, Tyr, and CP+Tyr groups were 44.68 ± 2.53, 32.31 ± 1.79, 45.23 ± 2.92, and 44.16 ± 1.08, respectively. The catalase level was the lowest in the CP group, and the difference between the other groups was statistically significant. The C, Tyr, and CP+Tyr groups were similar to each other in terms of catalase levels (*P*=0.001).

Studies have reported that cisplatin administration induces oxidative stress by causing lipid peroxidation and an imbalance in antioxidant defense systems [9, 14, 21]. In rats, a single dose of cisplatin has been observed to increase MDA levels and decrease antioxidants such as GSH, GSH-Px, and catalase, leading to damage in the ovary and uterus. Similarly, in this study, cisplatin administration resulted in increased MDA levels and decreased GSH levels, as well as reduced activities of GSH-Px and catalase in ovarian tissue. Numerous phytochemical compounds have been reported to exert beneficial effects on the side effects induced by cisplatin treatment [22].

Polyphenolic compounds are known to mitigate the side effects of chemotherapy drugs [23]. Natural antioxidants have been reported to have significant effects against oxidative stress-mediated ovarian damage [24, 25]. Tyrosol, a prominent natural antioxidant found in olive oil and wine, is highly stable, less prone to autooxidation, and maintains its antioxidant activity under critical conditions [12]. Furthermore, Tyrosol is a compound capable of exerting antioxidant effects by accumulating intracellularly [26]. Several studies have demonstrated that Tyrosol exerts significant antioxidant effects in various tissues, thereby reducing oxidative stress [12, 15, 27]. In this study, Tyrosol attenuated cisplatin-induced ovarian oxidative stress, particularly by decreasing MDA levels and enhancing catalase activity.

Ovarian TNF-α, IL-6, and IL-1β levels

In the CP group, TNF-α, IL-6, and IL-1β levels were measured at the highest values and were statistically different compared to the other groups. Also, the C, Tyr, and CP+Tyr groups were statistically similar.

In all groups, respectively (C, CP, Tyr, CP+Tyr), TNF-α levels were 48.16 ± 4.77; 86.23 ± 10.13; 47.28 ± 4.98; 51.67 ± 6.36 pg·mL^{-1}(*P*=0.002), IL-6 levels were 67.51 ± 5.15; 97.73 ± 4.09; 68.28 ± 4.57; 71.67 ± 5.84 pg·mL^{-1}(*P*=0.001), and IL-1β levels were 127.78 ± 9.16; 192.09 ± 11.57; 132.09 ± 9.15; 145.17 ± 11.65 pg·mL^{-1} (*P*=0.001), are shown in FIG. 3.

Inflammatory processes are reported to impair oocyte quality and cause fertility problems such as early menopause [28]. Cisplatin induces a strong inflammatory response in ovarian tissue by upregulating the expression of pro-inflammatory enzymes such as tumor necrosis factor and nuclear factor kappa-B [28]. Cisplatin stimulates various intracellular molecular pathways, leading to an increase in pro-inflammatory cytokine levels, such as TNF-α, IL-1β, and IL-6, and inducing inflammation through additional molecular mechanisms [29, 30]. According to a study, administering cisplatin (6 mg·kg^{-1}) twice, once a week, adversely affects ovarian function by influencing inflammatory processes [18]. In a study, it was observed that cisplatin increased the levels of inflammatory cytokines NFKB, TNF-α, IL-1β, IL-6, COX-2, and iNOS in the ovary [21]. In line with earlier research, this study observed an increase in ovarian TNF-α, IL-6, and IL-1β levels in rats

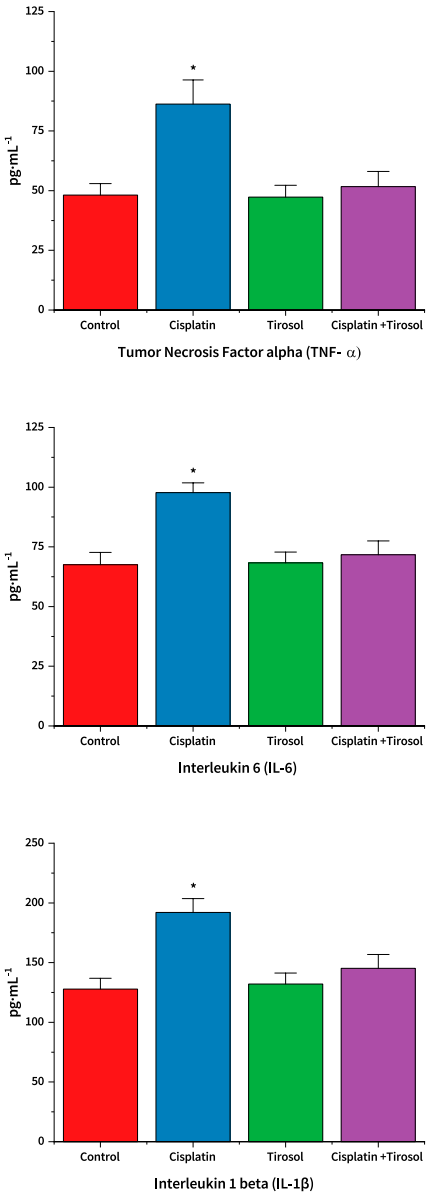

FIGURE 3. TNF-α, IL-6 and IL-1β levels in ovarian tissue. TNF-α, *P=0.002. IL-6, *P=0.001. IL-1β, *P=0.001

administered cisplatin. Cisplatin, one of the three chemotherapeutic agents frequently used in chemotherapy, significantly depletes ovarian follicular reserves by affecting various cellular components of the ovary, increasing the atresia of growing follicles, inducing damage in the stromal compartment, and causing inflammation.

To counteract these harmful effects, various compounds have been investigated as potential protective agents over the past 20 years [3]. Tyrosol is known to have anti-inflammatory effects [31, 32]. Furthermore, Tyrosol derivatives also exhibit strong anti-inflammatory properties [33]. In this study, Tyrosol was observed to mitigate cisplatin-induced ovarian damage by reducing elevated pro-inflammatory cytokine levels and restoring them to normal levels.

CONCLUSION

As a result, it can be concluded that Tyrosol has anti-inflammatory and antioxidant effects on the ovarian inflammatory and oxidative stress situation caused by cisplatin and has positive effects on ovarian activities. Future research on the effects of Tyrosol on other ovarian activities is thought to be beneficial.

Conflict of Interests

The authors declare no conflict of interest regarding the publication of this manuscript.

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