ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20230314

Does resveratrol reduce cisplatin-induced ovarian damage?

Baris Ciplak[1*], Eyup Gokhan Turmus[2], Ozlem Kara[3], Gulcin Daglioglu[4], Mehmet Murat Altindag[1], Yavuz Simsek[5], Yusuf Kenan Daglioglu[6], Mustafa Kara[7]

SUMMARY

OBJECTIVE: The objective of this study was to investigate the protectiveness of resveratrol on cisplatin-induced damage to the ovary using experimental models.

METHODS: A total of 30 female Wistar-Albino rats constituted the research material. The rats were categorized into three groups: Group 1 was administered one milliliter of 0.9% NaCl solution, Group 2 was administered 7.5 mg/kg cisplatin, and Group 3 was administered 7.5 mg/kg cisplatin and 10 mg/kg resveratrol. Ovaries were extirpated in all groups and subjected to biochemical and histopathological tests. Cisplatin-induced damage to ovarian tissue was graded and scored as the total histopathological findings score. The ovarian function was assessed using immunohistochemical staining for c-kit expression. Rats' malondialdehyde, catalase, and superoxide dismutase levels were determined.

RESULTS: The histopathological finding score was significantly higher in Group 2 than in other groups ($p<0.05$). The superoxide dismutase and catalase levels were significantly higher in Group 3 than in Group 2 ($p<0.001$ for both cases). The malondialdehyde level was significantly higher in Group 2 than in Group 3 ($p<0.001$).

CONCLUSION: The study findings demonstrated that resveratrol reduced ovarian injury and enhanced biochemical parameters following cisplatin-induced ovary damage in experimental models.

KEYWORDS: Cisplatin. Resveratrol. Rat. Ovary.

INTRODUCTION

Cisplatin is a platinum-based anticancer chemotherapy medication widely used to treat malignancies. However, it may adversely affect normal tissues and organs along with cancerous cells. The kidney, ovary, and liver are the main organs where cisplatin toxicity has been observed[1]. The accumulation of the platinum component of cisplatin may lead to a DNA complex, resulting in cell injury[2]. Elevated levels of reactive oxygen species and free radicals give rise to disruption of the cellular structure[3].

Resveratrol, an antioxidant found in fruits and red wine, has been shown to protect against free radical damage and is beneficial in the treatment of many diseases[4]. Den Hartogh et al.[5] reported that resveratrol enhances antioxidant activity by reducing inflammation and oxidative stress. Thus, resveratrol has become known as a cytoprotective nutrient. In addition, resveratrol, a free-radical scavenger, increases endothelial cell activity and exhibits potent antioxidant activity by blocking the DNA damage induced by free radicals, mainly through regulating major antioxidant enzymes[6].

Although advances in cancer treatments have improved survival, they cause premature ovarian failure, which presents as infertility in premenopausal women[7,8]. Both the increase in the frequency of female cancer and the fact that it is seen at a younger age have brought to the fore the negative effects of the chemotherapeutic drugs used on the reproductive system[7]. The invasiveness, high cost, and difficulty of implementing cryopreservation methods used for the preservation of ovarian tissue and the continuation of fertility limit their use. This situation has led to research into alternative treatment methods. A few experimental studies showed the beneficial effects of resveratrol on the number of primordial and primary follicles[9,10]. Extremely active nano-formulations of resveratrol regenerated the non-functional, chemoablated ovaries and testes in

[1]Malatya Training and Research Hospital, Clinic of Obstetrics and Gynecology – Malatya, Turkey.
[2]Yeşilyurt Hasan Çalık State Hospital, Clinic of Obstetrics and Gynecology – Malatya, Turkey.
[3]Ahi Evran University, Faculty of Medicine, Department of Hystology and Embryology – Kırsehir, Turkey.
[4]Çukurova University, Faculty of Medicine, Department of Biochemistry – Adana, Turkey.
[5]Biruni University, Faculty of Medicine, Department of Obstetrics and Gynecology – Istanbul, Turkey.
[6]Ahi Evran University, Faculty of Medicine, Department of Medical Microbiology – Kırsehir, Turkey.
[7]Ahi Evran University, Faculty of Medicine, Department of Obstetrics and Gynecology – Kırşehir, Turkey.
*Corresponding author: dr.baris_ciplak@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: Ahi Evran University Scientific Research Projects Unit.
Received on May 06, 2023. Accepted on May 07, 2023.

mice[11]. Resveratrol ameliorated oxidative stress, inflammation, and apoptosis secondary to cisplatin administration in female rats' ovarian and uterine tissues by preventing granulosa cell loss and controlling inflammation[7,8,12,13].

In view of the foregoing, this study was carried out to investigate the efficacy of resveratrol in reducing the ovarian damage caused by cisplatin using immunohistochemistry (IHC) and biochemical methods based on the hypothesis that resveratrol could protect the ovaries from the toxicity of cisplatin.

METHODS

Cisplatin (Ebewe-Liba, Istanbul, Turkey) and resveratrol (Sigma-Aldrich, Oakville, ON, Canada) were obtained from a pharmacy. Cisplatin was administered intraperitoneally at a dose of 7.5 mg/kg as previously described by Ibrahim et al.[8]. Intraperitoneal injections of resveratrol (10 mg/kg) were given based on the treatment protocol published previously[10].

Animals and experimental procedure

The study protocol was approved by the Kirikkale University Animal Experiments Local Ethics Committee (18.06.2020–2020/03-16) and supported by the Ahi Evran University Scientific Research Projects Unit (TIP.A4.21.001). A total of 30 female Wistar-Albino rats (150–220 g) aged 8–12 weeks were included in the study. All animals were kept for 1 week at approximately 24°C and fed an ad libitum laboratory diet. The rats were categorized into three groups, with 10 rats in each group. Group 1 (control group): A single intraperioneal dose of 1 ml/kg of 0.9% NaCl was given. Group 2 (cisplatin group): A single intraperioneal dose of 7.5 mg/kg cisplatin was given. Group 3 (cisplatin+resveratrol group): A single dose of 10 mg/kg resveratrol, followed by a single dose of 7.5 mg/kg cisplatin 1 h later, was administered intraperioneally.

Surgical procedures were initiated on the seventh day of the study. Ketamine/xylazine hydrochloride was used to achieve anesthesia in the rats. The ovaries on the right side were surgically removed and fixed in 10.0% formaldehyde. At the end of the procedure, the sacrification procedure was performed by cervical dislocation. Ovarian tissue samples were embedded in paraffin blocks and cut at 4 µm thickness. Sections were stained using hematoxylin and eosin (H&E) or with c-kit, also known as cluster of differentiation 117 (CD117) dye. Histopathological findings (HPF) were evaluated by a pathologist blinded to the experimental groups using a light microscope (Olympus CX41 microscope, Tokyo, Japan). At least 10 ovary areas were analyzed and assessed for IHC differences.

Intracardiac blood samples were centrifuged for biochemical analysis and stored in Eppendorf tubes at -80°C.

Immunohistochemistry

A polyclonal rabbit anti-human CD117 antibody (1:400; Dako, Glostrup, Denmark) was used to grade the immunohistochemical staining for c-kit expression. The results of c-kit staining (cytoplasmic/membranous staining in the ovarium) were scored as follows: negative (0), weak (1), moderate (2), and intense (3)[14].

A 5-point (0: None, 1: Minimal, 2: Mild, 3: Moderate, 4: Severe) scoring system was used in histopathological scoring. In this way, each area of the ovary was scored via a semi-quantitative analysis. The pigmentation, inflammation, fibrosis, congestion, and hemorrhage scores were used to determine the degree of damage, that is, the total HPF score.

Biochemistry

Blood samples were analyzed for malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) levels through absorbance using a spectrophotometer (Shimadzu UV 1800, Japan). A thiobarbituric acid test was used to calculate the MDA levels[15]. SOD enzyme activity was calculated as described by Marklund et al.[16], whereas CAT enzyme activity was calculated as described by Aebi[17].

Statistical analysis

Descriptive statistics obtained from the collected data were expressed as mean±standard deviation values in the case of continuous variables determined to conform to the normal distribution, as median and minimum-maximum values in the case of continuous variables determined not to conform to the normal distribution, and as numbers (n) and percentage (%) values in the case of categorical variables. The Fisher-Freeman-Halton test was used to compare the differences between categorical variables in RxC tables. The Kruskal-Wallis test was used to compare more than two independent groups where numerical variables did not conform to the normal distribution. In analyses featuring nonparametric tests, the differences between the groups were evaluated by the Dwass-Steel-Critchlow-Fligner test. The Jamovi project 2.2.5.0 and JASP 0.16.1 software packages were used in the statistical analyses. The probability (p) of ≤0.05 was deemed to indicate statistical significance.

RESULTS

Compared to the control subjects (Figure 1A), pigmentation, inflammation, fibrosis, congestion, and hemorrhage were

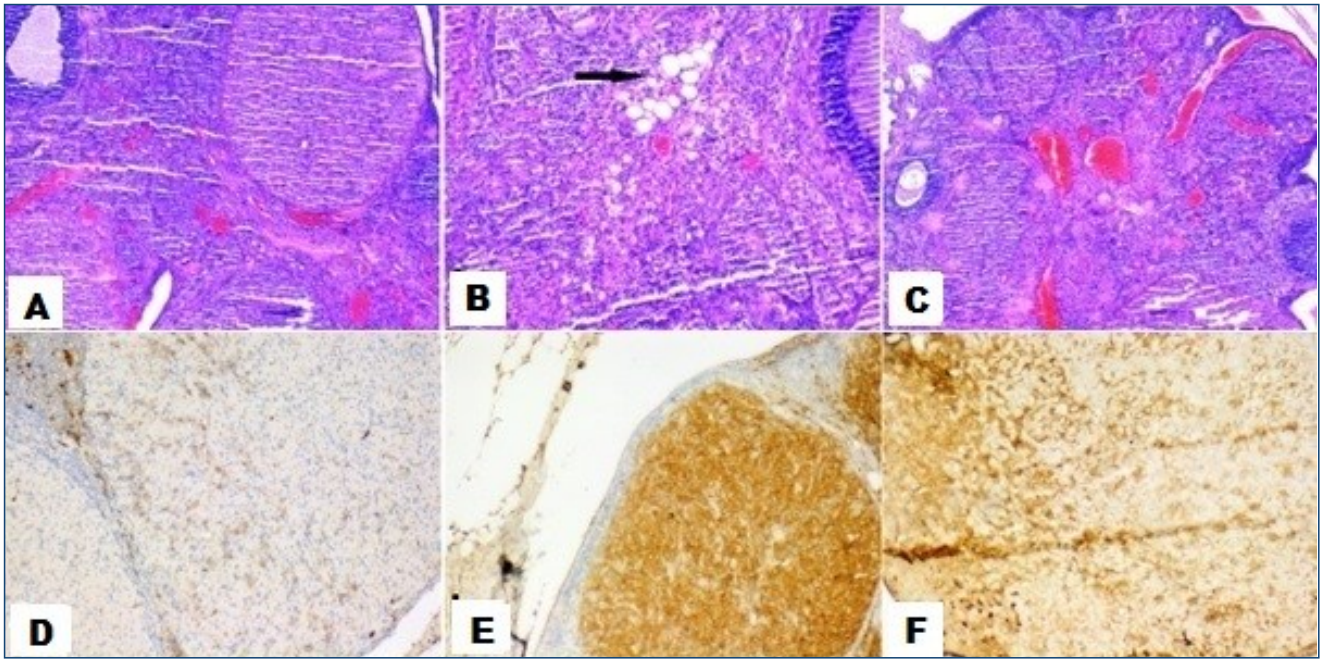

Figure 1. Light microscopic appearance of ovary **(A–C)** and immunohistochemical staining of rats by using c-kit **(D–F)**. **(A)** Minimally fibrosis and congestion in the ovarian stroma of the rat from the control group (H&E, ×50). **(B)** Lipoid cell storage (arrow), fibrosis, and lymphocyte infiltration in the ovarian stroma of the rat from the cisplatin group (H&E, ×100). **(C)** Mild fibrosis, congestion, and lymphocyte infiltration in the ovarian stroma of the rat from the cisplatin+resveratrol group (H&E, ×50). **(D)** Negative staining with c-kit (cd117) in the ovary of the rat from the control group (×100). **(E)** Focal 10% staining with c-kit (cd117) in the ovary of the rat from the cisplatin group (×100). **(F)** Focal 10% but less than cisplatin group staining with c-kit (cd117) in the ovary of the rat from the cisplatin + resveratrol group (×100).

detected in the ovarian tissues of the rats in Group 2 (Figure 1B), which were morphologically normal, and minimal fibrosis, congestion, and lymphocyte infiltration were observed in the rats in Group 3 (Figure 1C).

The total median HPF scores were 2, 12, and 6 in Groups 1, 2, and 3, respectively. There was a significant difference between the groups in HPH scores ($p<0.001$). The HPF score of Group 2 was significantly higher than those of Groups 3 ($p=0.003$) and 1 ($p<0.001$). The total HPF score of Group 3 was significantly higher than that of Group 1 ($p=0.004$). The comparison of the histopathological parameters revealed significant differences between the groups ($p<0.05$). There was no significant difference between Groups 2 and 3 in the distribution of pigmentation and fibrosis scores. As for congestion and hemorrhage, there were significantly more animals with low grades of congestion and hemorrhage in Group 3 than those in Group 2. The degree of inflammation was significantly higher in Group 2 than that in Group 3 (Table 1).

There were no animals with negative c-kit expression in Groups 2 and 3. However, there was a significant difference in the distribution of the c-kit expression grades between the three groups ($p<0.001$) and there was no significant difference in the percentage of different grades of c-kit expression in the ovarian tissues between Groups 2 and 3 (Table 2).

There were significant differences in serum MDA, SOD, and CAD levels between the groups ($p<0.001$). Group 1 had significantly lower levels of MDA and higher levels of SOD and CAD than Groups 2 and 3 ($p<0.001$ for all cases). The SOD and CAD levels were significantly higher in Group 3 than those in Group 2 ($p<0.001$ for both cases). In addition, Group 2 had significantly higher MDA levels than Group 3 ($p<0.001$) (Table 2).

Immunohistochemical staining of rats using c-kit dye revealed more ovarian damage in Group 2 (Figures 1D–F).

DISCUSSION

The study findings demonstrated that the degree of inflammation, congestion, and hemorrhage after cisplatin therapy was attenuated using resveratrol. Additionally, resveratrol increased the activities of SOD and CAT enzymes and reduced MDA activity. These findings have shown that resveratrol has protective potential against ovarian damage due to cisplatin-induced oxidative stress.

Table 1. Histopathological scoring of the findings evaluated in the ovarian tissue.

	Group 1 (Control) (n=10)	Group 2 (Cisplatin) (n=10)	Group 3 (Cisplatin+Resveratrol) (n=10)	p-value
Pigmentation‡				
None	7 (70.0)[a]	0 (0.0)[b]	0 (0.0)[b]	**<0.001***
Minimal	3 (30.0)[a]	3 (30.0)[a]	5 (50.0)[a]	
Mild	0 (0.0)[a]	6 (60.0)[b]	4 (40.0)[b]	
Moderate	0 (0.0)[a]	1 (10.0)[a]	1 (10.0)[a]	
Inflammation‡				
None	7 (70.0)[a]	0 (0.0)[b]	2 (20.0)[b]	**<0.001***
Minimal	3 (30.0)[a,b]	2 (20.0)[b]	7 (70.0)[a]	
Mild	0 (0.0)[a]	4 (40.0)[b]	1 (10.0)[a,b]	
Moderate	0 (0.0)[a]	4 (40.0)[b]	0 (0.0)[a]	
Fibrosis‡				
None	10 (100.0)[a]	0 (0.0)[b]	0 (0.0)[b]	**<0.001***
Minimal	0 (0.0)[a]	3 (30.0)[a,b]	7 (70.0)[b]	
Mild	0 (0.0)[a]	5 (50.0)[b]	3 (30.0)[a,b]	
Moderate	0 (0.0)[a]	1 (10.0)[a]	0 (0.0)[a]	
Severe	0 (0.0)[a]	1 (10.0)[a]	0 (0.0)[a]	
Congestion‡				
Minimal	7 (70.0)[a]	0 (0.0)[b]	6 (60.0)[a]	**0.002***
Mild	3 (30.0)[a]	3 (30.0)[a]	4 (40.0)[a]	
Moderate	0 (0.0)[a]	4 (40.0)[b]	0 (0.0)[a]	
Severe	0 (0.0)[a]	3 (30.0)[a]	0 (0.0)[a]	
Hemorrhage‡				
None	3 (30.0)[a]	0 (0.0)[a]	0 (0.0)[a]	**<0.001***
Minimal	6 (60.0)[a]	1 (10.0)[b]	7 (70.0)[a]	
Mild	1 (10.0)[a]	2 (20.0)[a]	3 (30.0)[a]	
Moderate	0 (0.0)[a]	6 (60.0)[b]	0 (0.0)[a]	
Severe	0 (0.0)[a]	1 (10.0)[a]	0 (0.0)[a]	
HPF total§	2.0 [1.0–6.0]	12.0 [6.0–17.0]	6.0 [4.0–9.0]	**<0.001***

‡n (%), §median [min–max]. HPF: histopathological findings. [a,b]Different letters showing significant differences between the groups. *Fisher Freeman Halton test. Bold indicates statistically significant values.

Table 2. Distribution of the c-kit expression levels and results of the biochemical parameters in the groups.

	Group 1 (Control) (n=10)	Group 2 (Cisplatin) (n=10)	Group 3 (Cisplatin+Resveratrol) (n=10)	p-value*
C-kit expression‡				
Negative	7 (70.0)[a]	0 (0.0)[b]	0 (0.0)[b]	**<0.001**
Weak	3 (30.0)[a]	1 (10.0)[a]	3 (30.0)[a]	
Intermediate	0 (0.0)[a]	4 (40.0)[b]	5 (50.0)[b]	
Strong	0 (0.0)[a]	5 (50.0)[b]	2 (20.0)[a,b]	
Biochemical parameters p-value**				
MDA§	3.2 [3.0–3.5]	8.2 [7.4–8.7]	5.0 [4.7–5.3]	**<0.001**
SOD§	30.1 [26.7–33.4]	12.3 [10.8–13.0]	19.4 [17.0–20.8]	**<0.001**
CAD§	65.9 [59.2–71.0]	17.1 [15.0–19.1]	37.1 [33.2–41.8]	**<0.001**

‡n (%). [a,b]Different letters showing significant differences between the groups. *Fisher Freeman Halton test. §median [min–max]. **Kruskal-Wallis H test, Dwass-Steel-Critchlow-Fligner test for pair-wise comparisons. Bold indicates statistically significant values.

Cisplatin has been used to treat cancers of many tissues and organs, such as the testes, ovaries, and lungs. However, its clinical use has been restricted due to its toxic effects. Dixit et al. reported gonadotoxicity and ovarian damage in approximately 40% of their patient cohort[18]. Many studies have shown that cisplatin results in ovarian tissue damage or injury[19,20]. Our results are also similar.

Resveratrol, a natural plant product, has been extensively studied. In one of these studies, Hascalik et al. investigated resveratrol in ovary torsion using a rat model and demonstrated that resveratrol reduced lipid peroxidation[21]. Antioxidants have often been used in experimental studies to antagonize the adverse effects caused by cisplatin. An example is resveratrol, which has been proven beneficial in ameliorating cisplatin-induced oxidative stress, inflammation, and apoptosis in ovarian and uterine tissues of female rats through its antioxidant, anti-inflammatory, and anti-apoptotic characteristics[8-10,22,23].

The resveratrol dosage used in studies varied from 5 to 50 mg/kg, depending on the target organ, including the liver, ovaries, or testes[9,10,12,24,25]. In comparison, the rats included in this study were administered 10 mg/kg/day of resveratrol. Consequently, it was concluded that resveratrol ameliorated, albeit not significantly, the severity of inflammation, congestion, and hemorrhage caused by cisplatin in the ovarian tissues. Nevertheless, the extent of the amelioration achieved by resveratrol provided sufficient evidence for its potential use against the toxic effects of cisplatin.

In a similar study conducted by Chinwe et al. resveratrol significantly increased SOD and CAT levels in the ovarian tissue in a dose-dependent manner and provided protection against the toxic effects of cisplatin by significantly reducing the MDA levels[9]. Administration of 10 mg/kg/day of resveratrol to the rats included in this study resulted in similar changes. The findings of this study have shown that it reduces oxidative stress by increasing SOD and CAT activity and decreasing MDA levels.

The histopathologic structure was more protected, as there was less inflammation, hemorrhage, and congestion in Group 3 compared to Group 2. The histopathological analysis revealed the highest scores in the group that received only cisplatin (Group 2), which decreased with the addition of resveratrol to the treatment regimen (Group 3). All these findings provided substantial evidence that resveratrol reduced and prevented cisplatin-induced ovarian toxicity in rats.

Compared to several growth factors, cytokines, and gonadal hormones, which are used to estimate normal ovarian function, c-kit expression is directly related to ovarian function and reserve. They thought that C-kit could be one of the new potential biomarkers of ovarian senescence[26]. In contrast, no significant difference was found between the groups investigated in this study in c-kit expression. More studies are needed to shed light on this subject.

The limitations of this study are as follows: first, it is a preclinical animal experiment. Second, there are no multi-dose groups of cisplatin and resveratrol. Third, due to the short experimental period, the parameters for evaluating the reproductive functions could not be studied (AMH, FSH, etc.). The strong aspect of this study is that the biochemical parameters were studied in blood instead of ovarian tissue in similar studies.

CONCLUSION

The study findings demonstrated that resveratrol reduced the histopathological damage and reversed the inflammatory response related to cisplatin. In our opinion, resveratrol has minimized the negative effects on ovarian tissue by reducing the oxidative stress caused by cisplatin. In order for the results of our study to be applied to medical practice, studies evaluating the effect of resveratrol and cisplatin at multiple doses in tumor tissue are also needed.

AUTHORS' CONTRIBUTIONS

BC: Conceptualization, Data curation, Formal Analysis, Project administration, Writing – original draft. **EGT:** Conceptualization, Data curation, Formal Analysis, Investigation, Writing – original draft. **OK:** Formal Analysis, Investigation, Methodology, Visualization, Writing – review & editing. **GD:** Formal Analysis, Investigation, Methodology, Writing – review & editing. **MMA:** Data curation, Writing – review & editing. **YS:** Conceptualization, Data curation, Project administration, Formal Analysis, Writing – review & editing. **YKD:** Data curation, Formal Analysis, Investigation, Methodology, Validation. **MK:** Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Writing – original draft.

REFERENCES

1. Ueki M, Ueno M, Morishita J, Maekawa N. Curcumin ameliorates cisplatin-induced nephrotoxicity by inhibiting renal inflammation in mice. J Biosci Bioeng. 2013;115(5):547-51. https://doi.org/10.1016/j.jbiosc.2012.11.007
2. Li X, Yang S, Lv X, Sun H, Weng J, Liang Y, et al. The mechanism of mesna in protection from cisplatin-induced ovarian damage in female rats. J Gynecol Oncol. 2013;24(2):177-85. https://doi.org/10.3802/jgo.2013.24.2.177
3. Boulikas T, Vougiouka M. Cisplatin and platinum drugs at the molecular level. Oncol Rep. 2003;10(6):1663-82. PMID: 14534679

4. Singh AP, Singh R, Verma SS, Rai V, Kaschula CH, Maiti P, et al. Health benefits of resveratrol: evidence from clinical studies. Med Res Rev. 2019;39(5):1851-91. https://doi.org/10.1002/med.21565
5. Hartogh DJ, Tsiani E. Health benefits of resveratrol in kidney disease: evidence from in vitro and in vivo studies. Nutrients. 2019;11(7):1624. https://doi.org/10.3390/nu11071624
6. Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J. Anti-inflammatory action and mechanisms of resveratrol. Molecules. 2021;26(1):229. https://doi.org/10.3390/molecules26010229
7. Eldani M, Luan Y, Xu PC, Bargar T, Kim SY. Continuous treatment with cisplatin induces the oocyte death of primordial follicles without activation. FASEB J. 2020;34(10):13885-99. https://doi.org/10.1096/fj.202001461RR
8. Ibrahim MA, Albahlol IA, Wani FA, Tammam AAE, Kelleni MT, Sayeed MU, et al. Resveratrol protects against cisplatin-induced ovarian and uterine toxicity in female rats by attenuating oxidative stress, inflammation and apoptosis. Chem Biol Interact. 2021;338:109402. https://doi.org/10.1016/j.cbi.2021.109402
9. Chinwe GS, Azuka OI, Adaeze NC. Resveratrol supplementation rescues pool of growing follicles and ovarian stroma from cisplatin-induced toxicity on the ovary in sprague-dawley rats: an experimental study. Int J Reprod Biomed. 2018;16(1):19-30. PMID: 29675484
10. Atli M, Engin-Ustun Y, Tokmak A, Caydere M, Hucumenoglu S, Topcuoglu C. Dose dependent effect of resveratrol in preventing cisplatin-induced ovarian damage in rats: an experimental study. Reprod Biol. 2017;17(3):274-80. https://doi.org/10.1016/j.repbio.2017.07.001
11. Chhabria S, Takle V, Sharma N, Kharkar P, Pansare K, Tripathi A, et al. Extremely active nano-formulation of resveratrol (XAR™) attenuates and reverses chemotherapy-induced damage in mice ovaries and testes. J Ovarian Res. 2022;15(1):115. https://doi.org/10.1186/s13048-022-01043-8
12. Wu H, Xue J, Di H, Lv C, Hao Y, Nie Z. Resveratrol improves ovarian function in aged rat by inhibiting oxidative stress and activating the sirt1. Gen Physiol Biophys. 2022;41(1):53-61. https://doi.org/10.4149/gpb_2021040
13. Said RS, Mantawy EM, Demerdash E. Mechanistic perspective of protective effects of resveratrol against cisplatin-induced ovarian injury in rats: emphasis on anti-inflammatory and anti-apoptotic effects. Naunyn Schmiedebergs Arch Pharmacol. 2019;392(10):1225-38. https://doi.org/10.1007/s00210-019-01662-x
14. Panzan MQ, Mattar R, Maganhin CC, Santos Simões R, Rossi AGZ, Motta ELA, et al. Evaluation of FAS and caspase-3 in the endometrial tissue of patients with idiopathic infertility and recurrent pregnancy loss. Eur J Obstet Gynecol Reprod Biol. 2013;167(1):47-52. https://doi.org/10.1016/j.ejogrb.2012.10.021
15. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351-8. https://doi.org/10.1016/0003-2697(79)90738-3
16. Marklund S, Marklund G. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. Eur J Biochem. 1974;47(3):469-74. https://doi.org/10.1111/j.1432-1033.1974.tb03714.x
17. Aebi H. Catalase in vitro. Methods Enzymol. 1984;105:121-6. https://doi.org/10.1016/S0076-6879(84)05016-3
18. Dixit M, Yang JL, Poirier MC, Price JO, Andrews PA, Arteaga CL. Abrogation of cisplatin-induced programmed cell death in human breast cancer cells by epidermal growth factor antisense RNA. J Natl Cancer Inst. 1997;89(5):365-73. https://doi.org/10.1093/jnci/89.5.365
19. Borovskaya T, Gol'dberg V, Pakhomova A, Perova A, Timina E. Morphological and functional state of rat ovaries in the early and late periods after injection of vepesid. Bull Exp Biol Med. 2006;141(5):645-7. https://doi.org/10.1007/s10517-006-0242-9
20. Yeh J, Kim BS, Peresie J. Protection against cisplatin-induced ovarian damage by the antioxidant sodium 2-mercaptoethanesulfonate (mesna) in female rats. Am J Obstet Gynecol. 2008;198(4):463.e1-6. https://doi.org/10.1016/j.ajog.2007.12.027
21. Hascalik S, Celik O, Turkoz Y, Hascalik M, Cigremis Y, Mizrak B, et al. Resveratrol, a red wine constituent polyphenol, protects from ischemia-reperfusion damage of the ovaries. Gynecol Obstet Invest. 2004;57(4):218-23. https://doi.org/10.1159/000076760
22. Kulhan N, Kulhan M, Türkler C, Ata N, Kiremitli T, Kiremitli S, et al. Effect of lycopene on oxidative ovary-damage induced by cisplatin in rats. Gen Physiol Biophys. 2019;38(3):253-8. https://doi.org/10.4149/gpb_2019006.
23. Algandaby MM. Quercetin attenuates cisplatin-induced ovarian toxicity in rats: emphasis on anti-oxidant, anti-inflammatory and anti-apoptotic activities. Arabian J Chem. 2021;14(7):103191. https://doi.org/10.1016/j.arabjc.2021.103191
24. Aly HA, Eid BG. Cisplatin induced testicular damage through mitochondria mediated apoptosis, inflammation and oxidative stress in rats: impact of resveratrol. Endocr J. 2020;67(9):969-80. https://doi.org/10.1507/endocrj.EJ20-0149
25. Paunović MG, Matić MM, Stanković VD, Milošević MD, Jevtić VV, Trifunović SR, et al. Evaluation of toxic effects of novel platinum (IV) complexes in female rat liver: potential protective role of resveratrol. Cell Biochem Biophys. 2021;79(1):141-52. https://doi.org/10.1007/s12013-020-00953-y
26. Park MJ, Ahn JW, Kim KH, Bang J, Kim SC, Jeong JY, et al. Prediction of ovarian aging using ovarian expression of BMP15, GDF9, and C-KIT. Exp Biol Med. 2020;245(8):711-9.https://doi.org/10.1177/1535370220915826