Farabi Tıp Dergisi 1(1): 1-7, 2022
Farabi Medical Journal 1(1): 1-7, 2022

FARABİ TIP DERGİSİ
FARABI MEDICAL JOURNAL

Özgün Makale
Original Article

https://dergipark.org.tr/tr/pub/farabimedj

The Effect of Chlorogenic Acid on 5-Fluorouracil-Induced Oxidative Damage in Rat Ovarian Tissue

Klorojenik Asidin Sıçan Yumurtalık Dokusunda 5-Florourasil ile İndüklenen Oksidatif Hasar Üzerine Etkisi

Ahmet Mentese[1], Selim Demir[2*], Nihal Turkmen Alemdar[3,4], Yuksel Aliyazicioglu[1], Orhan Deger[1]

[1]*Karadeniz Technical University, Faculty of Medicine, Department of Medical Biochemistry, 61080 Trabzon, Turkey.*
[2]*Karadeniz Technical University, Faculty of Health Sciences, Department of Nutrition and Dietetics, 61080 Trabzon, Turkey.*
[3]*Karadeniz Technical University, Graduate School of Health Sciences, Department of Medical Biochemistry, 61080 Trabzon, Turkey.*
[4]*Recep Tayyip Erdogan University, Vocational School of Health Services, Department of Medical Services and Techniques, 53100 Rize, Turkey.*

**Corresponding author e-mail: selim-demir@hotmail.com*

[1]*https://orcid.org/0000-0003-2036-5317*
[2]*https://orcid.org/0000-0002-1863-6280*
[3]*https://orcid.org/0000-0002-8913-8692*
[4]*https://orcid.org/0000-0001-9474-4307*
[5]*https://orcid.org/0000-0003-3584-6324*

ABSTRACT

5-fluorouracil (5-FU) is a potent anticancer agent, but its significant tissue toxicity associated with increased oxidative stress and inflammation can limit its clinical use. Chlorogenic acid (CGA) is a dietary polyphenol found in a variety of foods and beverages, including coffee, apple, pear, strawberry and grape. It was aimed to evaluate the therapeutic effects of CGA on 5-FU-induced ovotoxicity through oxidative stress and inflammation parameters in this study. Thirty female Sprague-Dawley rats were divided into 5 groups with equal numbers of subjects (n=6): control, 5-FU (100 mg/kg), 5-FU+CGA (1.5 mg/kg), 5-FU+CGA (3 mg/kg) and CGA (3 mg/kg). The ovarian tissue levels of malondialdehyde (MDA), total oxidant status (TOS), total antioxidant status (TAS), 8-hydroxy-2'-deoxyguanosine (8-OHdG), catalase (CAT) and interleukin-6 (IL-6) were determined using commercial spectrophotometric kits. While 5-FU treatment increased MDA, TOS, 8-OHdG and IL-6 levels in ovarian tissue, it significantly decreased TAS and CAT levels ($p<0.05$). These parameters, indicating 5-FU-induced toxicity, were significantly reversed with CGA administrations in a dose-dependent manner ($p<0.05$). The results support the view that CGA may be a useful modulator in attenuating 5-FU-induced ovotoxicity.

Keywords: 5-fluorouracil, Chlorogenic acid, Inflammation, Ovotoxicity, Oxidative stress

ÖZET

5-florourasil (5-FU) güçlü bir antikanser ajandır, ancak artan oksidatif stres ve inflamasyon ile ilişkili önemli doku toksisitesi klinik kullanımını sınırlayabilmektedir. Klorojenik asit (CGA) kahve, elma, armut, çilek ve üzüm dahil olmak üzere çeşitli yiyecek ve içeceklerde bulunan bir diyet polifenolüdür. Bu çalışmada, CGA'nın 5-FU ile indüklenen yumurtalık dokusu toksisitesi üzerine terapötik etkilerinin oksidatif stres ve inflamasyon parametreleri açısından değerlendirilmesi amaçlandı. Otuz Sprague-Dawley ırkı dişi sıçan eşit sayıda denek (n=6) içeren 5 gruba ayrıldı: kontrol, 5-FU (100 mg/kg), 5-FU+CGA (1.5 mg/kg), 5-FU+CGA (3 mg/kg) ve CGA (3 mg/kg). Yumurtalık dokularında malondialdehit (MDA), toplam oksidan durum (TOS), toplam antioksidan durum (TAS), 8-hidroksi-2'-deoksiguanozin (8-OHdG), katalaz (CAT) ve interlökin-6 (IL-6) seviyeleri ticari spektrofotometrik kitler kullanılarak belirlendi. 5-FU uygulaması yumurtalık dokusunda MDA, TOS, 8-OHdG ve IL-6 düzeylerini artırırken, TAS ve CAT düzeylerini anlamlı olarak azalttı ($p<0.05$). 5-FU ile indüklenen toksisiteyi gösteren bu parametreler, CGA tedavisi ile doza bağlı bir şekilde anlamlı derecede tersine çevrildi ($p<0.05$). Sonuçlar, CGA'nın 5-FU ile indüklenen yumurtalık dokusu toksisitesini azaltmada faydalı bir modülatör olabileceği görüşünü desteklemektedir.

Anahtar Kelimeler: 5-florourasil, İnflamasyon, Klorojenik asit, Oksidatif stres, Yumurtalık dokusu toksisitesi

Geliş Tarihi/Received Date: 06.11.2022 | *Kabul Tarihi/Accepted Date: 21.11.2022*

INTRODUCTION

Cancer is a growing public health problem and responsible for millions of deaths worldwide each year.[1] Chemotherapy is a form of drug therapy that aims to kill fast-growing tumor cells with powerful chemicals in the body.[2] 5-Fluorouracil (5-FU) is a chemotherapeutic drug that is widely used in the treatment of colorectal, esophageal and gastric cancers.[3] The antitumor effects of 5-FU are mainly due to its suppression of DNA and RNA synthesis by inhibiting thymidylate synthase.[2] The toxic effect of 5-FU is dose dependent and also varies from patient to patient, which can sometimes lead to discontinuation of therapy. Common intolerable, serious and painful side effects of 5-FU-based chemotherapy are mucositis, hepatorenal toxicity, diarrhea, myelosuppression, cardiotoxicity, dermatitis and reproductive toxicity.[2,4] The reproductive toxicity of 5-FU is generally associated with developmental block, malformation and ovarian damage in females. The cytotoxicity of 5-FU potentially contributes to ovarian dysfunction and puts patients at risk for menopausal complications and infertility.[2] It has been suggested that 5-FU-induced tissue toxicity is associated with increased oxidative stress and inflammation due to increased formation of reactive oxygen species (ROS), lipid peroxidation and decreased glutathione levels.[1] It is therefore very important to determine the compounds that will eliminate 5-FU-induced ovotoxicity and to use them after chemotherapy in female patients for the continuation of fertility.[4]

Natural products have become very popular in recent years with their success in complementary therapy. Due to the phenolic compounds of natural products, they exhibit antioxidant, anticancer, anti-inflammatory, antimicrobial and immunomodulatory effects.[5] Chlorogenic acid (CGA) is one of the most common phenolic acids in the human diets and is commonly found in a variety of natural products, such as tea, beans, coffee, mulberry fruits, cocoa, citrus fruits, apple and pears.[6] It has many beneficial biological effects, such as antidiabetic, anti-obesity, antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, cardioprotective, hepatoprotective and renoprotective.[6,7] There are increasing evidences in the literature that CGA reduces the toxicity of various chemotherapeutic agents, such as methotrexate, 5-FU and cyclophosphamide, in testicular, kidney and ovarian tissues through its antioxidant and anti-inflammatory potential.[5,8,9] Although the protection of female reproductive health against 5-FU toxicity in chemotherapy is crucial for the maintenance of fertility, to our knowledge, there are no studies of the therapeutic effect of CGA on 5-FU-induced ovarian damage in an experimental rat model. The aim of this study was therefore to determine whether CGA could provide a therapeutic effect against 5-FU-induced ovarian damage and to elucidate the underlying molecular mechanisms in terms of oxidative stress and inflammation.

METHODS

Chemicals

Phosphate buffered saline (PBS) tablet, dimethyl sulfoxide (DMSO), phosphoric acid, thiobarbituric acid, 1,1,3,3-tetramethoxypropane, sodium carbonate, 5-FU and CGA were purchased from Sigma-Aldrich (St. Louis, MO, USA). All reagents used were of analytical grade and of the highest purity.

Animals

The experiments were performed in accordance with the Guidelines for Animal Research from the National Institute of Health and were approved by the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol no: 2022/15). In this experimental study, 30 female Sprague-Dawley rats (weighing 150±25 g and 8-10 weeks old) obtained from the Surgical Practice Research Center of Karadeniz Technical University were used. The estrus stages of the rats were determined using staining the vaginal smear sample according to the Papanicolaou staining procedure and examining the cell types under the microscope, and only rats whose estrus stage was confirmed were included in the study.[10]

Experimental design

Rats were housed for two weeks at standard temperature (22±2°C) conditions and on a 12 h light/dark cycle to adapt to the environment. Then, animals were divided into 5 groups (6 in each group) as follows:

Group I (Control): The rats received saline in first day intraperitoneally (ip) and DMSO (ip) for three consecutive days.

Group II (5-FU): 5-FU was applied as a single dose (in saline, 100 mg/kg, ip) on day 1 of the experiment followed by DMSO (ip) for 3 days.

Group III and IV (5-FU+CGA; 1.5 and 3 mg/kg): 5-FU was applied as a single dose (in saline, 100 mg/kg, ip) on day 1 of the experiment. Rats received CGA (1.5 and 3 mg/kg, ip) for 3 days from day 1.

Group V (CGA *per se*): Rats received the equivalent volumes of saline (ip) on day 1 and were treat with CGA (3 mg/kg, ip) for 3 days from day 1. CGA (dissolved with DMSO)[11,12] and 5-FU[13,14] doses used in this study were determined according to previous related studies. The animals were fasted overnight after the final treatment and sacrificed by cervical dislocation on the 5th day, after which the ovaries were removed from the animals in each group.[15] The ovarium tissues were excised and stored at -80℃ for subsequent biochemical analysis.

Biochemical analysis

The tissue samples were homogenized at 9500 rpm in 2 mL of PBS using a homogenizer (IKA, T25 Ultra-Turrax, Staufen, Germany). The supernatant portions were separated by means of centrifugation at 1800xg for 10 min at 4°C and used in the biochemical analysis. Protein levels of the supernatants were determined using a commercial kit (Pierce BCA Protein Assay Kit, Thermo Scientific, Rockford, IL) according to the manufacturer's instructions and calculated as mg/mL bovine serum albumin equivalent. All biochemical parameters measured in the supernatants were proportioned to the amount of protein and expressed as per mg protein. Malondialdehyde (MDA) levels of tissue samples were determined according to the method developed by Mihara and Uchiyama.[16] 1,1,3,3-tetramethoxypropane was used as a standard and tissue MDA levels were expressed as nmol/mg protein. Tissue total oxidant status (TOS) and total antioxidant status (TAS) levels were determined using commercial colorimetric kits (Rel Assay Diagnostics, Gaziantep, Turkey) according to the manufacturer's recommendations. The TOS/TAS ratio was used as the oxidative stress index (OSI) and was calculated using the formula:[17]

$$\text{OSI (arbitrary unit)} = \frac{\text{TOS (µmoL hydrogen peroxide equivalent/L)}}{\text{TAS (µmoL trolox equivalent/L)}} \text{ x } 100$$

Tissue catalase (CAT), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and interleukin-6 (IL-6) levels were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (Fine Biotech Co. Ltd, Wuhan, China) according to the manufacturer's recommendations. CAT, 8-OHdG and IL-6 levels were expressed mIU/mg protein, ng/mg protein and pg/mg protein, respectively.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (Version 23.0, NY, USA). The compliance of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. Comparisons of the groups were carried out using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. Statistical significance was set at $p<0.05$.

RESULTS

There was a significant increase in the ovarian MDA, TOS and OSI levels in the 5-FU-treated group compared to the control group (p=0.011, p=0.003 and p=0.001, respectively). CGA (1.5 mg/kg) treatment only provided a significant improvement in OSI levels compared to 5-FU group (p=0.045). However, CGA (3 mg/kg) treatment decreased the levels of MDA, TOS and OSI significantly compared with 5-FU group (p=0.012, p=0.003 and p=0.001, respectively). While the TAS value was significantly decreased in the 5-FU group compared to the control group (p=0.015), CGA (3 mg/kg) treatment significantly restored the TAS value compared to the 5-FU group (p=0.043). (Table 1). We observed sigficantly increased 8-OHdG and IL-6 levels and decreased CAT levels in only 5-FU-treated animals as compared to control animals (p=0.0001, p=0.003 and p=0.0001, respectively). CGA (1.5 mg/kg) treatment only provided a significant improvement in 8-OHdG levels compared to 5-FU group (p=0.02). However, CGA (3 mg/kg) treatment restored the levels of 8-OHdG, IL-6 and CAT significantly compared with 5-FU group (p=0.0001, p=0.004 and p=0.0001, respectively). There was a statistically significant difference between CGA doses in terms of 8-OHdG and CAT parameters (p=0.01 and p=0.0001, respectively) (Figure 1). In addition, there was no statistically significant difference between the control group and the CGA (3 mg/kg, *per se*) groups in terms of biochemical parameters (p>0.05) (Table 1 and Figure 1).

Table 1. Effect of CGA and 5-FU on oxidative stress markers of ovarian tissues

	Control	5-FU	5-FU+CGA (1.5 mg/kg)	5-FU+CGA (3 mg/kg)	CGA (3 mg/kg)
MDA (nmol/mg protein)	29.7±5.9	65.8±31.9[a]	38.2±17.1	30.2±8.2[b]	27.9±9.3
TOS (μM H_2O_2 equivalent/L)	10.3±1.6	39.3±19.7[a]	22.1±18.0	10.9±1.4[b]	11.6±1.2
TAS (mM trolox equivalent/L)	1.03±0.6	0.33±0.2[a]	0.55±0.3	1.1±0.4[b]	0.97±0.3
OSI (arbitrary unit)	1.25±0.5	15.4±10.3[a]	5.95±4.3[b]	1.22±0.7[b]	1.30±0.4

5-FU: 5-fluorouracil, CGA: chlorogenic acid, MDA: malondialdehyde, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index. P-values according to one-way ANOVA test, post-hoc Tukey test. Data were expressed as mean±SD.
[a]p<0.05 compared with control group,
[b]p<0.05 compared with 5-FU group.

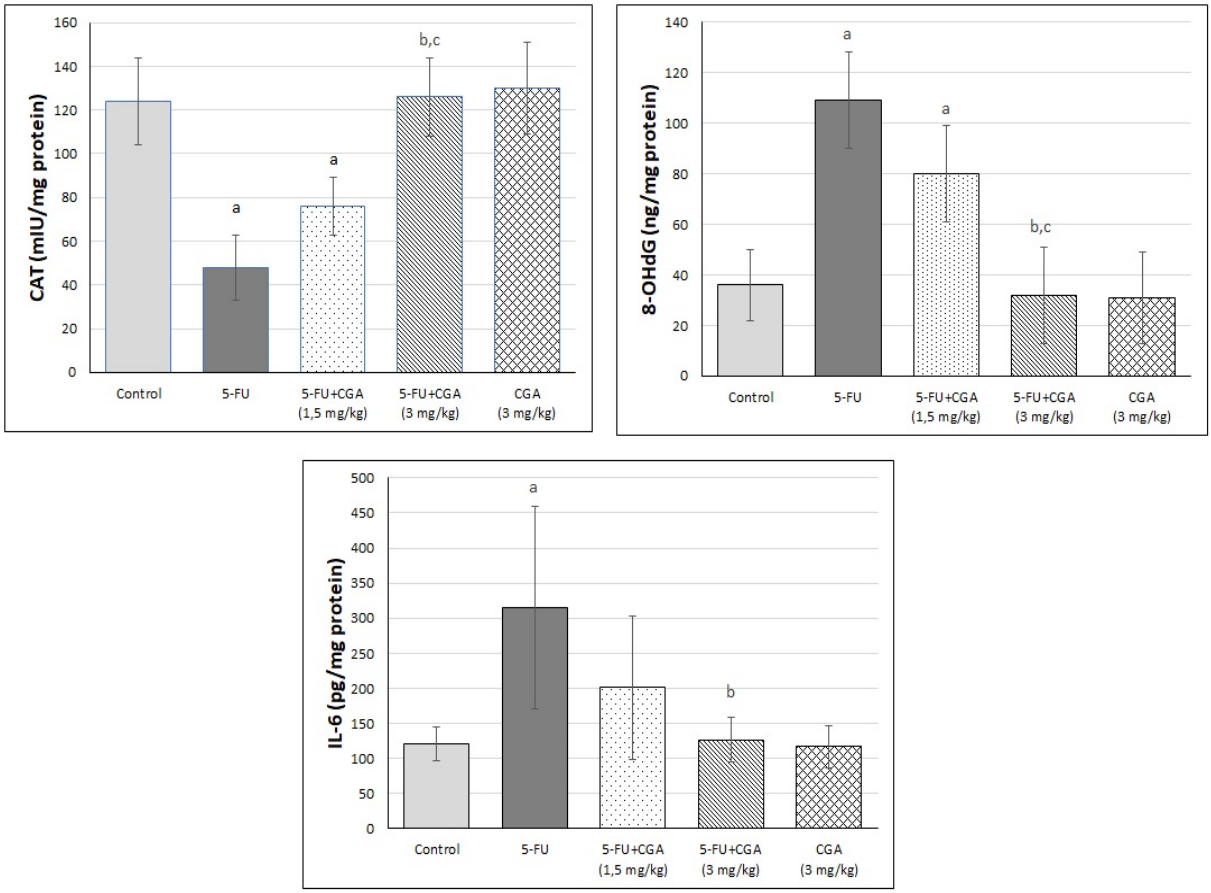

Figure 1. Effect of CGA and 5-FU on CAT, 8-OHdG and IL-6 levels of ovarian tissues. All values were expressed as mean±SD. [a]Statistically significant from control group, [b]Statistically significant from 5-FU group (p<0.05), [c]Statistically significant from 5-FU+CGA (1.5 mg/kg) group (p<0.05) using one-way ANOVA followed by Tukey's post-hoc analysis.

DISCUSSION

The reproductive toxicity of antineoplastic agents used for cancer treatment is a very important point to consider as its potential impact on the health of offspring and female patients.[2] Although 5-FU is one of the most commonly used chemotherapeutics, the discovery that it can cause reproductive system toxicity in recent years,[18,19] has accelerated the search for molecules that can eliminate 5-FU-induced toxicity.[20] It is emphasized that the toxicity of chemotherapeutics in normal tissues is due to the induction of inflammation, apoptosis and oxidative stress damage.[3] We therefore aimed to investigate the therapeutic effect of CGA, which is known for its effective antioxidant properties, on 5-FU-induced ovarian damage in an experimental rat model for the first time. 5-FU-induced lipid peroxidation and free radical generation leading to cell membrane damage are considered as the main mechanism behind its toxic effects.[21] MDA, one of the end products of lipid peroxidation, is a highly toxic

compound that cross-links cellular macromolecules, such as protein and DNA, giving them antigenic properties.[22] It is well known that two of the crucial parameters for evaluating redox balance in biological systems are TAS and TOS. While TAS determines the overall ROS scavenging ability in a biological sample, TOS can be defined as the cumulative amount of total oxidants in the sample. For the quantitative assessment of redox homeostasis disorders, the OSI, which is called the "gold indicator of oxidative stress", is used.[23] Oxidative stress also increases DNA damage and 8-OHdG is one of the main products of DNA oxidation.[3] The increased MDA, TOS, OSI and 8-OHdG levels and decreased TAS levels in 5-FU-treated rats indicates that ROS-induced oxidative cell damage is mediated by 5-FU toxicity. These findings are consistent with data from previous studies demonstrating that 5-FU increases oxidative stress and DNA damage.[3,9,24,25] CGA treatments restored these levels in a dose-dependent manner. The alleviation of oxidative stress and DNA damage parameters by CGA treatments with may be due to the free radical scavenging potential of CGA.[6,7] Consistent with our results, CGA has previously been shown to prevent chemotherapeutic-induced tissue damage by inhibiting oxidative stress in experimental models.[8,11,26]

The antioxidant system constantly tries to keep the endogenous and exogenous ROS production in balance, preventing tissue damage.[10] CAT is the enzyme with the highest known turnover number and catalyzes the reduction of hydrogen peroxide to water.[27] Our findings showed that systemic administration of 5-FU suppressed CAT activity in ovarian tissue. It can be said that this situation may have made the ovarian tissue more prone to 5-FU-induced damage. This is consistent with the results of previous experimental studies on 5-FU-induced tissue damage.[21,28] However, treatments with CGA significantly increased the levels of CAT in a dose-dependent manner. Similarly, CGA has previously been shown to prevent chemical-induced tissue damage by increasing the levels of antioxidant enzymes in experimental models.[5,26]

Inflammation is a physiological response of the organism to tissue damage caused by exogenous or endogenous factors. However, an unregulated and excessive inflammatory response can lead to excessive tissue damage, resulting in chronic disease states.[29] Increasing evidences have revealed that inflammation plays an important role in the occurrence of 5-FU-related tissue damage.[28,30] IL-6 is a very important cytokine involved in the pro-inflammatory process and there is a positive correlation between increased IL-6 levels and the degree of inflammation.[31,32] Our findings revealed that high IL-6 levels appeared in the ovarian tissue of rats exposed only to 5-FU, and CGA treatments significantly reduced these values in a dose-dependent manner. This improvement appears to be due to the anti-inflammatory property of CGA, which has often been demonstrated.[6] Consistent with our results, CGA has previously been shown to prevent chemical-induced tissue damage by inhibiting inflammation in experimental models.[11,32-34]

CONCLUSION

This study provides biochemical evidence for the therapeutic efficacy of CGA against 5-FU-induced ovarian toxicity. Extensive additional research is required to better understand the therapeutic effect of CGA against 5-FU-induced ovarian damage. Thus, significant progress can be made regarding the use of CGA in the elimination of chemotherapy-related complications.

Acknowledgement

The authors wish to thank Sait Al and Ibrahim Aydin from Surgical Practice Research Center of Karadeniz Technical University for professional assistance with the experimental studies.

Authorship contribution statement

Consept and desing: AM.
Acquisition of data: AM, SD and NTA.
Analysis and interpretation of data: AM, SD and YA.
Drafting of the manuscript: AM and SD.
Critical revision of the manuscript for important intellectual content: YA and OD.
Statistical analysis: AM.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study was approved by the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol no: 2022/15) and performed according to the animal research reporting of *in vivo* experiments (ARRIVE) guidelines.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

No financial support was received for this research.

REFERENCES

1. Jurczyk M, Król M, Midro A, Kurnik-Łucka M, Poniatowski A, Gil K. Cardiotoxicity of fluoropyrimidines: Epidemiology, mechanisms, diagnosis, and management. J Clin Med. 2021; 10(19): 4426. DOI: 10.3390/jcm10194426.
2. Naren G, Guo J, Bai Q, Fan N, Nashun B. Reproductive and developmental toxicities of 5-fluorouracil in model organisms and humans. Expert Rev Mol Med. 2022; 24: e9. DOI: 10.1017/erm.2022.3.
3. Zeng D, Wang Y, Chen Y, et al. Angelica polysaccharide antagonizes 5-FU-induced oxidative stress injury to reduce apoptosis in the liver through Nrf2 pathway. Front Oncol. 2021; 11: 720620. DOI: 10.3389/fonc.2021.720620.
4. Al-Asmari AK, Khan AQ, Al-Masri N. Mitigation of 5-fluorouracil-induced liver damage in rats by vitamin C via targeting redox-sensitive transcription factors. Hum Exp Toxicol. 2016; 35(11): 1203-1213. DOI: 10.1177/0960327115626583.
5. Alkis I, Ekin S, Yildirim S, Bakir A, Eser G, Firat M. Evaluation of the protective effect of chlorogenic acid and *Rhabdosciadium anatolyi* against cyclophosphamide-induced ovarian toxicity in the rat with histopathological and immunohistochemical findings. Kafkas Univ Vet Fak Derg. 2020; 26(6): 757-763. DOI: 10.9775/kvfd.2020.24305.
6. Naveed M, Hejazi V, Abbas M, et al. Chlorogenic acid (CGA): A pharmacological review and call for further research. Biomed Pharmacother. 2018; 97: 67-74. DOI: 10.1016/j.biopha.2017.10.064.
7. Lu H, Tian Z, Cui Y, Liu Z, Ma X. Chlorogenic acid: A comprehensive review of the dietary sources, processing effects, bioavailability, beneficial properties, mechanisms of action, and future directions. Compr Rev Food Sci Food Saf. 2020; 19(6): 3130-3158. DOI: 10.1111/1541-4337.12620.
8. Vardi N, Parlakpinar H, Ates B, Otlu A. The preventive effects of chlorogenic acid against to testicular damage caused by methotrexate. Turkiye Klinikleri J Med Sci. 2010; 30(2): 507-513.
9. Rashid S, Sultana S. Chlorogenic acid represses 5-fluorouracil induced renal oxidative stress, apoptosis and inflammation in murine model. Free Radic Biol Med. 2016; 100: S128-S129. DOI: 10.1016/j.freeradbiomed.2016.10.336.
10. Mentese A, Alemdar NT, Livaoglu A, Demir EA, Aliyazicioglu Y, Demir S. Suppression of cisplatin-induced ovarian injury in rats by chrysin: An experimental study. J Obstet Gynaecol. 2022; DOI: 10.1080/01443615.2022.2130201, In Press.
11. Domitrović R, Cvijanović O, Šušnić V, Katalinić N. Renoprotective mechanisms of chlorogenic acid in cisplatin-induced kidney injury. Toxicology. 2014; 324: 98-107. DOI: 10.1016/j.tox.2014.07.004.
12. Park SH, Baek SI, Yun J, et al. IRAK4 as a molecular target in the amelioration of innate immunity-related endotoxic shock and acute liver injury by chlorogenic acid. J Immunol. 2015; 194(3): 1122-1130. DOI: 10.4049/jimmunol.1402101.
13. Zhang S, Liu Y, Xiang D, et al. Assessment of dose-response relationship of 5-fluorouracil to murine intestinal injury. Biomed Pharmacother. 2018; 106: 910-916. DOI: 10.1016/j.biopha.2018.07.029.
14. Narayana K, D'Souza UJ, Sanyal AK, Rao KP. 5-fluorouracil (5-FU) induces the formation of giant cells and sloughing of seminiferous epithelium in the rat testis. Indian J Physiol Pharmacol. 2000; 44(3): 317-322.
15. Demir EA, Mentese A, Livaoglu A, Alemdar NT, Demir S. Ameliorative effect of gallic acid on cisplatin-induced ovarian toxicity in rats. Drug Chem Toxicol. 2021; DOI: 10.1080/01480545.2021.2011312, In Press.
16. Mihara M, Uchiyama M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal Biochem 1978; 86(1): 271-278. DOI: 10.1016/0003-2697(78)90342-1.
17. Demir S, Kazaz IO, Kerimoglu G, et al. Astaxanthin protects testicular tissue against torsion/detorsion-induced injury via suppressing endoplasmic reticulum stress in rats. J Invest Surg. 2022; 35(5): 1044-1049. DOI: 10.1080/08941939.2021.1995540.
18. Lambouras M, Liew SH, Horvay K, Abud HE, Stringer JM, Hutt KJ. Examination of the ovotoxicity of 5-fluorouracil in mice. J Assist Reprod Genet. 2018; 35: 1053-1060. DOI: 10.1007/s10815-018-1169-6.
19. Stringer JM, Swindells EOK, Zerafa N, Liew SH, Hutt KJ. Multidose 5-fluorouracil is highly toxic to growing ovarian follicles in mice. Toxicol Sci. 2018; 166(1): 97-107. DOI: 10.1093/toxsci/kfy189.
20. Zhang QY, Wang FX, Jia KK, Kong LD. Natural product interventions for chemotherapy and radiotherapy-induced side effects. Front Pharmacol. 2018; 9: 1253. DOI: 10.3389/fphar.2018.01253.
21. Rashid S, Ali N, Nafees S, Ahmad ST, Hasan SK, Sultana S. Abrogation of 5-flourouracil induced renal toxicity by bee propolis via targeting oxidative stress and inflammation in Wistar rats. J Pharm Res. 2013; 7(2): 189-194.
22. Kazaz IO. Demir S, Kerimoglu G, et al. Chlorogenic acid ameliorates torsion/detorsion-induced testicular injury via decreasing endoplasmic reticulum stress. J Pediatr Urol. 2022; 18(3): 289.e1-289.e7. DOI: 10.1016/j.jpurol.2022.02.013.
23. Kazaz IO, Demir S, Kerimoglu G, et al. Effect of chrysin on endoplasmic reticulum stress in a rat model of testicular torsion. J Invest Surg. 2022; 35(5): 1106-1111. DOI: 10.1080/08941939.2021.2015489.
24. Al-Asmari AK, Khan AQ, Al-Qasim AM, Al-Yousef Y. Ascorbic acid attenuates antineoplastic drug 5-fluorouracil induced gastrointestinal toxicity in rats by modulating the expression of inflammatory mediators. Toxicol Rep. 2015; 2: 908-916. DOI: 10.1016/j.toxrep.2015.06.006.
25. Gelen V, Şengül E, Yıldırım S, Senturk E, Tekin S, Kükürt A. The protective effects of hesperidin and curcumin on 5-fluorouracil-induced nephrotoxicity in mice. Environ Sci Pollut Res Int. 2021; 28(34): 47046-47055. DOI: 10.1007/s11356-021-13969-5.
26. Ali N, Rashid S, Nafees S, et al. Protective effect of chlorogenic acid against methotrexate induced oxidative

stress, inflammation and apoptosis in rat liver: An experimental approach. Chem Biol Interact. 2017; 272: 80-91. DOI: 10.1016/j.cbi.2017.05.002.
27. Demir EA, Mentese A, Kucuk H, Alemdar NT, Demir S. *p*-Coumaric acid alleviates cisplatin-induced ovarian toxicity in rats. J Obstet Gynaecol Res. 2022; 48(2): 411-419. DOI: 10.1111/jog.15119.
28. Arab HH, Salama SA, Maghrabi IA. Camel milk ameliorates 5-fluorouracil-induced renal injury in rats: Targeting MAPKs, NF-κB and PI3K/Akt/eNOS pathways. Cell Physiol Biochem. 2018; 46(4): 1628-1642. DOI: 10.1159/000489210.
29. Liang N, Kitts DD. Role of chlorogenic acids in controlling oxidative and inflammatory stress conditions. Nutrients 2016; 8: 16. DOI: 10.3390/nu8010016.
30. Rodrigues D, de Souza T, Coyle L, et al. New insights into the mechanisms underlying 5-fluorouracil-induced intestinal toxicity based on transcriptomic and metabolomic responses in human intestinal organoids. Arch Toxicol. 2021; 95: 2691-2718. DOI: 10.1007/s00204-021-03092-2.
31. Xue Y, Huang F, Tang R, et al. Chlorogenic acid attenuates cadmium-induced intestinal injury in Sprague-Dawley rats. Food Chem Toxicol. 2019; 133: 110751. DOI: 10.1016/j.fct.2019.110751.
32. Gao W, Wang C, Yu L, et al. Chlorogenic acid attenuates dextran sodium sulfate-induced ulcerative colitis in mice through MAPK/ERK/JNK pathway. Biomed Res Int. 2019; 2019: 6769789. DOI: 10.1155/2019/6769789.
33. Shi H, Dong L, Jiang J, et al. Chlorogenic acid reduces liver inflammation and fibrosis through inhibition of toll-like receptor 4 signaling pathway. Toxicology. 2013; 303: 107-114. DOI: 10.1016/j.tox.2012.10.025.
34. Guo Z, Li J. Chlorogenic acid prevents alcohol-induced brain damage in neonatal rat. Transl Neurosci. 2017; 8: 176-181. DOI: 10.1515/tnsci-2017-0024.

To Cite: Mentese A, Demir S, Alemdar NT, Aliyazicioglu Y, Deger O. The effect of chlorogenic acid on 5-fluorouracil-induced oxidative damage in rat ovarian tissue. Farabi Med J. 2022; 1(1): 1-7.