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Therapeutic Effect of Sinapic Acid against 5-Fluorouracil-Induced Oxidative Stress and Inflammation in Rat Ovarium: An Experimental Approach

Sıçan Yumurtalık Dokusunda 5-Florourasil ile Uyarılan Oksidatif Stres ve İnflamasyona Karşı Sinapik Asitin Terapötik Etkisi: Deneysel Bir Yaklaşım

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ABSTRACT

Tissue toxicity caused by 5-fluorouracil (5-FU) is associated with increased reactive oxygen species and inflammatory cytokines. Sinapic acid (SA) has both antioxidant and anti-inflammatory activities. Although SA has been shown to ameliorate chemical-induced tissue damage in various experimental models, its effects against 5-FU-induced ovarian damage have not yet been investigated. It was therefore aimed to evaluate the therapeutic potential of SA against 5-FU-induced ovarian damage in rats, together with the mechanisms of oxidative stress and inflammation in this study for the first time. Thirty rats were distributed into five groups: control, 5-FU (100 mg/kg) 5-FU+SA (2.5 and 5 mg/kg) and SA (5 mg/kg). 5-FU was applied to rats intraperitoneally on the 1st day of experiments and then SA was administrated for 3 consecutive days. The levels of lipid peroxidation [malondialdehyde (MDA)], oxidative stress (total oxidant status (TOS) and oxidative stress index (OSI)], antioxidant system [total antioxidant status (TAS), and catalase (CAT)], DNA damage [8-hydroxy-2'-deoxyguanosine (8-OHdG)] and inflammatory [interleukin-6 (IL-6)] markers in ovarian tissues were determined using spectrophotometric methods. It was determined that a single dose of 5-FU administration in rats significantly increased oxidative stress and inflammation in the ovarian tissue and suppressed the antioxidant system compared to the control group ($p<0.05$). It was revealed that SA significantly suppressed ovarian inflammation by decreasing IL-6 levels, attenuates DNA damage by decreasing 8-OHdG levels, and also provides restoration of oxidative stress by decreasing MDA, TOS and OSI levels and increasing TAS and CAT levels in a dose-dependent manner. In conclusion, we found that SA exhibits therapeutic effects against 5-FU-induced ovarian damage. These findings suggest that SA may be a potentially useful agent for protection against chemotherapeutic-induced ovarian injury.

Keywords: 5-fluorouracil, Inflammation, Ovarian damage, Oxidative stress, Rat, Sinapic acid

ÖZET

5-florourasil (5-FU)'nun neden olduğu doku toksisitesi, artan reaktif oksijen türleri ve inflamatuar sitokinler ile ilişkilidir. Sinapik asit (SA) bir fenolik asittir ve hem antioksidan hem de anti-inflamatuar aktivitelere sahiptir. Çeşitli deneysel modellerde SA'nın kimyasal kaynaklı doku hasarını iyileştirdiği gösterilmiş olmasına rağmen, 5-FU kaynaklı yumurtalık hasarına karşı etkileri henüz araştırılmamıştır. Bu nedenle bu çalışmada SA'nın sıçanlarda 5-FU ile indüklenen yumurtalık hasarına karşı terapötik potansiyelinin oksidatif stres ve inflamasyon mekanizmaları ile birlikte ilk kez değerlendirilmesi amaçlandı. Otuz sıçan beş gruba ayrıldı: kontrol, 5-FU (100 mg/kg), 5-FU+SA (2,5 ve 5 mg/kg) ve SA (5 mg/kg). Sıçanlara deneylerin 1. günü intraperitoneal yoldan 5-FU, ardından 3 gün boyunca SA uygulandı. Yumurtalık lipid peroksidasyon seviyeleri [malondialdehit (MDA)], oksidatif stres (toplam oksidan durum (TOS) ve oksidatif stres indeksi (OSI)], antioksidan sistem [toplam antioksidan durum (TAS) ve katalaz (CAT)], DNA hasarı [8-hidroksi-2'-deoksiguanozin (8-OHdG)] ve inflamatuvar [interlökin-6 (IL-6)] belirteçlerinin düzeyleri spektrofotometrik yöntemlerle belirlendi. Sıçanlarda tek doz 5-FU uygulamasının kontrol grubuna göre yumurtalık dokusunda oksidatif stresi ve inflamasyonu anlamlı olarak arttırdığı ve antioksidan sistemi baskıladığı belirlendi ($p<0.05$). SA'nın IL-6 düzeylerini düşürerek over inflamasyonunu önemli ölçüde baskıladığı, 8-OHdG düzeylerini düşürerek DNA hasarını azalttığı ve ayrıca MDA, TOS ile OSI düzeylerini düşürerek ve TAS ile CAT düzeylerini artırarak oksidatif stresin restorasyonunu doza bağımlı bir şekilde sağladığı ortaya konuldu ($p<0.05$). Sonuç olarak, SA'nın 5-FU ile indüklenen yumurtalık hasarına karşı terapötik etkiler gösterdiğini bulduk. Bu bulgular SA'nın kemoterapötik kaynaklı yumurtalık hasarına karşı koruma için potansiyel olarak yararlı bir ajan olabileceğini düşündürmektedir.

Anahtar Kelimeler: 5-florourasil, İnflamasyon, Oksidatif stress, Rat, Sinapik asit, Yumurtalık hasarı

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INTRODUCTION

Cancer is the leading cause of death worldwide.[1] Although chemotherapy is one of the most widely used treatments to treat various types of cancer, the cytotoxic effect of chemotherapeutic drugs on rapidly proliferating normal cells remains an unsolved problem.[2] With the increasing improvements in cancer survival rates with chemotherapy, reducing the significant long-term side effects that affect patients following treatment is critical. For women, damage from chemotherapy to the reproductive system results in premature menopause and/or infertility.[3] 5-fluorouracil (5-FU) is a widely used anti-neoplastic agent against a variety of tumors, including carcinomas of the gastrointestinal tract, breast, head and neck.[4] 5-FU exhibits its effect by inhibiting RNA and DNA synthesis in rapidly dividing cells, including cancer cells.[3] The anticancer effect of 5-FU is due to its ability to inhibit the enzyme thymidylate synthase and to form intermediates, such as fluorouridine triphosphate and fluorodeoxyuridine triphosphate, that are incorporated into RNA and DNA. All these mechanisms suppress DNA repair mechanisms that lead to cell death.[4] However, 5-FU treatment can lead to significant toxic conditions resulting in myelotoxicity, neurotoxicity, cardiotoxicity and mucositis.[3] Although information on reproductive toxicity is limited since 5-FU is usually administered with other chemotherapeutic drugs, it has been shown that 5-FU administration causes ovarian damage in experimental animals in recent years.[5-7] It is well documented that overproduction of reactive oxygen species (ROS) and inflammatory mediators play a vital role in the toxic manifestations induced by 5-FU. Therefore, it is suggested that the use of agents with antioxidant and anti-inflammatory potential may be beneficial in eliminating 5-FU-related tissue toxicity.[2]

The phytochemicals, found in plants, are reported to have numerous benefits in the treatment of cancer, liver ailments, diabetes, heart diseases, kidney ailments, and many more. The use of plant-based products has therefore increased significantly all over the world.[8] Phenolic compounds have attracted the attention of researchers as their powerful antioxidant properties can protect the body against free radicals and oxidative stress in recent years.[9] Sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid, SA) is a natural herbal compound included in the phenolic acid group. It is found in various natural products, such as wheat, rice, spices, oil seeds, vegetables, citrus fruits, cereals and vinegar.[10,11] Antioxidant, anti-inflammatory, anticancer, antihyperglycemic, antidiabetic, hepatoprotective, cardioprotective, renoprotective, neuroprotective, anxiolytic and antibacterial activities of SA have been demonstrated in previous studies.[8,10] The tissue protective role of SA against dimethylnitrosamine, cisplatin, bleomycin and cyclophosphamide induced injury have also been previously reported.[9,11-13] Therefore, we hypothesized that SA could effectively suppress 5-FU-induced ovotoxicity and sought to explore the therapeutic efficacy of SA against 5-FU-induced ovarian damage and to uncover the mechanisms underlying this in the current research for the first time.

METHODS

Chemicals and kits

Phosphate buffered saline (PBS) tablet, phosphoric acid, thiobarbituric acid, 1,1,3,3-tetramethoxypropane, dimethyl sulfoxide (DMSO), SA and 5-FU were purchased from Sigma-Aldrich (St. Louis, MO, USA). All chemicals used were of analytical grade. The bicinchoninic acid (BCA) assay kit used for the protein levels of tissue samples determination was purchased from Thermo Scientific (Rockford, IL). Total oxidant status (TOS) and total antioxidant status (TAS) kits were purchased from Rel Assay Diagnostics (Gaziantep, Turkey). Rat catalase (CAT), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and interleukin-6 (IL-6) enzyme-linked immunosorbent assay (ELISA) kits were purchased from Fine Biotech Co. Ltd (Wuhan, China).

Animals

Thirty adult female Sprague-Dawley rats with weighting 150-170 g and aged 7-8 weeks were obtained from the Surgical Practice Research Centre of Karadeniz Technical University. Animals were fed standard rat chow with free access to tap water and maintained under light-darkness for 12 h in a room temperature (22±3°C) and humidity (50±20%) controlled facility. Animals received humane care in accordance with the guidelines of the US National Institutes of Health, and the all stages of experiments were approved by the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol no: 2022/14).

Experimental design

Thirty rats were assigned to 5 groups (n=6/group) designated as: control, 5-FU (100 mg/kg), 5-FU+SA (2.5 mg/kg), 5-FU+SA (5 mg/kg) and SA (5 mg/kg)

groups. 5-FU and SA were administered intraperitoneally (i.p.) to rats. Group 1: Animals in the control group were treated with saline on the first day and DMSO for the following three days. Group 2: Animals in the 5-FU group were administered 5-FU (100 mg/kg) on the first day and DMSO for the following three days. Group 3 and 4: The rats were administered 5-FU (100 mg/kg) on the first day and 2.5 mg/kg and 5 mg/kg of SA for the following three days, respectively. Group 5: Animals in the SA *per se* group were administered saline on the first day and SA (5 mg/kg) for the following three days. 5-FU and SA were prepared by dissolving with saline and DMSO, respectively. The doses of 5-FU[6,14] and SA[15,16] administered to the rats were determined by considering the previous literature. At the end of the fifth days, all rats were sacrificed with cervical dislocation and their ovaries were excised and stored at -80°C for biochemical analysis.[17]

Biochemical analysis

Ovarian tissue was cut into small pieces and homogenized with 2 mL of ice-cold PBS (pH: 7.4) using a homogenizer (IKA, T25 Ultra-Turrax, Staufen, Germany). Residues were removed from the homogenate by centrifugation at 1800xg for 10 min at 4°C. The protein concentrations of the supernatants were determined using a commercial BCA assay kit using bovine serum albumin as the reference standard.

Malondialdehyde (MDA) levels of ovarian tissues were determined by a previously published method.[18] 1,1,3,3-tetramethoxypropane was used as a standard and tissue MDA levels were expressed as nmol/mg protein.

Tissue TOS and TAS levels were determined using commercial colorimetric kits according to the manufacturer's recommendations. The TOS/TAS ratio was used as the oxidative stress index (OSI) and was calculated using the formula[19]:

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

Tissue CAT, 8-OHdG and IL-6 levels were determined using commercial ELISA kits according to the manufacturer's recommendations. The absorbance measurement of biochemical markers measured by ELISA method was performed using a microplate reader (Molecular Devices Versamax, Sunnyvale, CA, USA) at 450 nm wavelength. 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

The levels of MDA, TOS, OSI, 8-OHdG and IL-6 in the ovarian tissue were significantly enhanced in 5-FU-induced rats compared with normal control rats (112%, p=0.02; 545%, p=0.0001; 1550%, p=0.003; 591%, p=0.0001 and 352%, p=0.001, respectively). SA (2.5 mg/kg) treatment significantly reduced only the levels of 8-OHdG compared with 5-FU-induced rats without treatment (39%, p=0.008). However, SA (5 mg/kg) treatment significantly reduced the levels of MDA, TOS, OSI, 8-OHdG and IL-6 compared with 5-FU-induced rats without treatment (48%, p=0.038; 78%, p=0.002; 92%, p=0.003; 81%, p=0.0001 and 78%, p=0.001, respectively).

The TAS and CAT levels were significantly decreased by 55% (p=0.02) and 49% (p=0.019), respectively in the ovarian tissue of 5-FU-induced rats compared with normal control rats. Treatment with SA (5 mg/kg) significantly increased the reduced levels of TAS and CAT by 55% (p=0.02) and 46% (p=0.038), respectively compared with only 5-FU-treated rats.

In addition, treatment with SA (5 mg/kg) alone did not show any significant change in the any biochemical parameter levels compared with the control group (p>0.05) (Table 1).

Table 1. Effect of SA treatments on ovarian oxidative stress, DNA damage and inflammatory parameters

	Control	5-FU	5-FU+SA (2.5 mg/kg)	5-FU+SA (5 mg/kg)	SA (5 mg/kg)
MDA (nmol/mg protein)	32.7±14.9	69.3±23.8[a]	41.7±25.8	35.9±16.7[b]	29.2±7.6
TOS (μM H_2O_2 equivalent/L)	9.80±0.68	63.2±35.3[a]	36.8±25.0	13.8±6.26[b]	11.1±4.00
TAS (mM trolox equivalent/L)	0.88±0.21	0.40±0.18[a]	0.60±0.33	0.88±0.32[b]	0.82±0.15
OSI (arbitrary unit)	1.17±0.28	19.3±13.7[a]	9.72±9.63	1.62±0.54[b]	1.35±0.55
8-OHdG (ng/mg protein)	17.2±8.0	118.9±22.4[a]	73.0±35.0[a,b]	22.6±12.7[b,c]	20.9±17.1
CAT (mIU/mg protein)	148.8±46.9	76.3±13.0[a]	103.4±18.3	142.3±38.1[b]	158.5±52.9
IL-6 (pg/mg protein)	132.4±46.2	598.9±213.2[a]	347.5±332.7	134.3±32.3[b]	129.4±41.7

5-FU: 5-fluorouracil, SA: sinapic acid, MDA: malondialdehyde, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, 8-OHdG: 8-hydroxy-2'-deoxyguanosine, CAT: catalase, IL-6: interleukin-6.
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,
c $p<0.05$ compared with 5-FU+SA (2.5 mg/kg) group.

DISCUSSION

5-FU is one of the most widely used chemotherapeutic drugs in the treatment of various types of cancer. However, tissue toxicity is one of the most important side effects of 5-FU. Because 5-FU acts specifically on tumor cells, but also on normally proliferating cells, which ultimately results in severe toxicity.[20] Tissue toxicity due to 5-FU is thought to be initially caused by increased oxidative stress and associated inflammatory and apoptotic processes.[21] Based on the fact that 5-FU administration causes acute ovarian damage in experimental models in recent years, it was aimed for the first time to evaluate the effects of SA on the ovarian tissue of rats administered 5-FU through oxidative stress and inflammation parameters in the current study.

There is a constant production of ROS in the human body as a result of metabolic processes.[22] In the normal physiological state, ROS production in the body is balanced by the cleansing antioxidant system. This balance is disturbed due to overproduction of ROS and/or insufficiency of the antioxidant system, and this is called oxidative stress.[24] It has been revealed that oxidative stress plays a role in the etiopathogenesis of many pathological conditions, such as aging, cancer, cardiovascular diseases and chemical-induced damage.[10,26] Scientific evidences have shown that oxidative stress plays a central role in mediating 5-FU-induced tissue toxicity. Excessive production of ROS causes membrane lipid peroxidation, carbohydrate, protein and DNA damage and ultimately oxidative cellular destruction.[26] MDA is one of the end products of lipid peroxidation, and an increase in MDA indicates an increase in oxidative stress and a decrease in antioxidant enzymes.[27] 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.[28] Oxidative stress also increases DNA damage, and 8-OHdG is one of the main products of DNA oxidation.[29] Removal of free radicals in biological systems is achieved through enzymatic and non-enzymatic antioxidants, which act as the main defense systems against free radicals.[1,30] CAT, an antioxidant enzyme, prevents oxidative stress-induced cell damage by catalyzing the breakdown reaction of H_2O_2 to water and oxygen.[29] The role of oxidative stress and oxidative stress-induced DNA damage in 5-FU-induced ovarian toxicity was evaluated by analyzing markers of MDA, TOS, TAS, OSI and 8-OHdG in this study. In the current study, ovarian tissue of rats treated with 5-FU exhibited higher levels of MDA, TOS, OSI and 8-OHdG, but lower levels of TAS and CAT, compared to normal rats. These findings are consistent with data from previous studies showing that 5-FU increases oxidative stress and DNA damage and suppresses the antioxidant system.[2,6,20,26,31] SA treatments (2.5 and 5 mg/kg) significantly and dose-dependently attenuated oxidative stress, as demonstrated by decreased lipid peroxidation, DNA damage and renewed antioxidant levels compared to 5-FU-treated rats alone. SA is considered an important chain-breaking antioxidant that functions efficiently as

a radical scavenger. The role of SA as an antioxidant is related to its hydrogen atom donating ability and its ability to stabilize phenoxyl radicals generated through the conjugate system. It is also reported that the antioxidant function of SA is much more important than ferulic acid and caffeic acid.[8] Alleviation of oxidative stress and DNA damage parameters by SA treatments suggested that SA is due to its free radical scavenging potential and hydrogen atom donating ability. These results confirmed the results of previous reports.[11,27,32,33]

Oxidative stress and inflammatory processes are closely related, and inflammatory cytokines play an important role in 5-FU-induced acute tissue injury.[21] 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.[6] The role of inflammation in 5-FU-induced ovarian toxicity was therefore evaluated by analyzing marker of IL-6 in this study. Ovarian tissue of rats treated with 5-FU exhibited higher levels of IL-6 compared to normal rats. These findings were consistent with data from previous studies showing that 5-FU increases tissue inflammation levels.[20,21,26,34] However, IL-6 levels were found to be significantly reduced in the ovarian tissue of rats which received SA treatment for 3 days after 5-FU injection. This alleviation may be due to the effective anti-inflammatory activity of SA resulting from its ability to regenerate the antioxidant system.[33] Consistent with our results, previous studies have reported that SA can exert beneficial effects in various models of chemical-induced organ damage, through its ability to modulate pro-inflammatory cytokines, including IL-6, tumor necrosis factor-alpha, interleukin-1 beta, myeloperoxidase and nuclear factor-kappa B.[12,13,27,35,36]

CONCLUSION

We demonstrated using an *in vivo* model that SA can exert an ovoprotective effect against 5-FU-induced ovarian injury for the first time. This is most likely due to the antioxidant and anti-inflammatory activity of SA. The use of natural antioxidants as potential therapeutic agents in the abolition of chemotherapeutic-induced tissue damage is of increasing interest. Our data suggest that SA may also be useful in ameliorating 5-FU-induced ovarian injury. However, more extensive preclinical studies are required to prove its clinical efficacy.

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Authorship contribution statement

Consept and desing: SD.

Acquisition of data: SD, AL, EAD and NTA.

Analysis and interpretation of data: SD, AM, EAD and YA.

Drafting of the manuscript: SD.

Critical revision of the manuscript for important intellectual content: YA.

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: 2022/14) 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.

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REFERENCES

1. 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; 42(8): 3584-3590. DOI: 10.1080/01443615.2022.2130201.
2. 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.
3. 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.
4. Hodroj K, Barthelemy D, Lega JC, et al. Issues and limitations of available biomarkers for fluoropyrimidine-based chemotherapy toxicity, a narrative review of the literature. ESMO Open. 2021; 6(3): 100125. DOI: 10.1016/j.esmoop.2021.100125.
5. Almeida JZ, Lima LF, Vieira LA, et al. 5-Fluorouracil disrupts ovarian preantral follicles in young C57BL6J mice. Cancer Chemother Pharmacol. 2021; 87(4): 567-578. DOI: 10.1007/s00280-020-04217-7.

6. 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.
7. 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.
8. Pandi A, Kalappan VM. Pharmacological and therapeutic applications of sinapic acid-an updated review. Mol Biol Rep. 2021; 48(4): 3733-3745. DOI: 10.1007/s11033-021-06367-0.
9. Shin DS, Kim KW, Chung HY, Yoon S, Moon JO. Effect of sinapic acid against dimethylnitrosamine-induced hepatic fibrosis in rats. Arch Pharm Res. 2013; 36(5): 608-618. DOI: 10.1007/s12272-013-0033-6.
10. Chen C. Sinapic acid and its derivatives as medicine in oxidative stress-induced diseases and aging. Oxid Med Cell Longev. 2016; 2016: 3571614. DOI: 10.1155/2016/3571614.
11. Rezaei S, Hosseinimehr SJ, Zargari M, Malekshah AK, Mirzaei M, Amiri FT. Protective effects of sinapic acid against cyclophosphamide-induced testicular toxicity via inhibiting oxidative stress, caspase-3 and NF-kB activity in BALB/c mice. Andrologia. 2021; 53(10): e14196. DOI: 10.1111/and.14196.
12. Ansari MA. Sinapic acid modulates Nrf2/HO-1 signaling pathway in cisplatin-induced nephrotoxicity in rats. Biomed Pharmacother. 2017; 93: 646-653. DOI: 10.1016/j.biopha.2017.06.085.
13. Raish M, Ahmad A, Ahmad Ansari M, et al. Sinapic acid ameliorates bleomycin-induced lung fibrosis in rats. Biomed Pharmacother. 2018; 108: 224-231. DOI: 10.1016/j.biopha.2018.09.032.
14. 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.
15. Shahmohamady P, Eidi A, Mortazavi P, Panahi N, Minai-Tehrani D. Effect of sinapic acid on memory deficits and neuronal degeneration induced by intracerebroventricular administration of streptozotocin in rats. Pol J Pathol. 2018; 69(3): 266-277. DOI: 10.5114/pjp.2018.79546.
16. Zych M, Kaczmarczyk-Sedlak I, Wojnar W, Folwarczna J. The effects of sinapic acid on the development of metabolic disorders induced by estrogen deficiency in rats. Oxid Med Cell Longev. 2018; 2018: 9274246. DOI: 10.1155/2018/9274246.
17. 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. 2023; 46(1): 97-103. DOI: 10.1080/01480545.2021.2011312.
18. 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.
19. Demir S, Kazaz IO, Aliyazicioglu Y, et al. Effect of ethyl pyruvate on oxidative state and endoplasmic reticulum stress in a rat model of testicular torsion. Biotech Histochem. 2020; 95(4): 317-322. DOI: 10.1080/10520295.2019.1695947.
20. 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.
21. Liu JH, Hsieh CH, Liu CY, Chang CW, Chen YJ, Tsai TH. Anti-inflammatory effects of Radix Aucklandiae herbal preparation ameliorate intestinal mucositis induced by 5-fluorouracil in mice. J Ethnopharmacol. 2021; 271: 113912. DOI: 10.1016/j.jep.2021.113912.
22. Demir EA, Demir S, Turkmen N, Turan I. The effect of *Rosa pimpinellifolia* extract on the proliferation of human tumor cells. KSU J Agric Nat. 2021; 24(6): 1170-1176. DOI: 10.18016/ksutarimdoga.vi.848137.
23. Aliyazicioglu Y, Demir S, Yaman SO, et al. Phytochemical analysis of *Dorycnium pentaphyllum* and its antiproliferative effect on cervix cancer cells. KSU J Agric Nat. 2019; 22(Suppl 2): 365-373. DOI: 10.18016/ksutarimdoga.vi.579938.
24. Turan I, Demir S, Aliyazicioglu R, et al. Dimethyl sulfoxide extract of *Dianthus carmelitarum* induces S phase arrest and apoptosis in human colon cancer cells. Nutr Cancer. 2019; 71(7): 1181-1188. DOI: 10.1080/01635581.2019.1598563.
25. 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.
26. Bin Jardan YA, Ansari MA, Raish M, et al. Sinapic acid ameliorates oxidative stress, inflammation, and apoptosis in acute doxorubicin-induced cardiotoxicity via the NF-κB-mediated pathway. Biomed Res Int. 2020; 2020: 3921796. doi:10.1155/2020/3921796.
27. 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.
28. 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.
29. Rehman MU, Ali N, Rashid S, et al. Alleviation of hepatic injury by chrysin in cisplatin administered rats: Probable role of oxidative and inflammatory markers. Pharmacol Rep. 2014; 66(6): 1050-1059. DOI: 10.1016/j.pharep.2014.06.004.
30. 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. DOI: 10.1016/j.jopr.2013.03.003.
31. Singh HP, Singh TG, Singh R. Sinapic acid attenuates cisplatin-induced nephrotoxicity through peroxisome proliferator-activated receptor gamma agonism in rats. J Pharm Bioallied Sci. 2020; 12(2): 146-154. DOI: 10.4103/jpbs.JPBS_220_19.

32. Ahmad A, Alkharfy KM, Bin Jardan YA, et al. Sinapic acid mitigates methotrexate-induced hepatic injuries in rats through modulation of Nrf-2/HO-1 signaling. Environ Toxicol. 2021; 36(7): 1261-1268. DOI: 10.1002/tox.23123.
33. 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.
34. Raish M, Shahid M, Bin Jardan YA, et al. gastroprotective effect of sinapic acid on ethanol-induced gastric ulcers in rats: Involvement of Nrf2/HO-1 and NF-κB signaling and antiapoptotic role. Front Pharmacol. 2021; 12: 622815. DOI: 10.3389/fphar.2021.622815.
35. Shahid M, Raish M, Ahmad A, et al. Sinapic acid ameliorates acetic acid-induced ulcerative colitis in rats by suppressing inflammation, oxidative stress, and apoptosis. Molecules. 2022; 27(13): 4139. DOI: 10.3390/molecules27134139.

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