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Evaluation of Therapeutic Effect of Chrysin against 5-Fluorouracil-Induced Ovarian Damage in Rats

Sıçanlarda 5-Florourasil Kaynaklı Yumurtalık Hasarına Karşı Krisinin Terapötik Etkisinin Değerlendirilmesi

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ABSTRACT

5-fluorouracil (5-FU) is an effective and widely used chemotherapeutic agent to treat various malignancies, but its therapeutic use is limited due to dose-related tissue toxicity. Many studies have confirmed that oxidative stress and inflammation play a major role in the pathogenesis of 5-FU-induced damage in the various tissues. Chrysin (CHS), a natural flavone, exhibits various beneficial activities, including antioxidant, anti-inflammatory and anticancer. The aim of this study was to determine the therapeutic effect of CHS against 5-FU-induced oxidative stress and inflammation in the ovary tissue of rats for the first time. Thirty female rats were divided into 5 groups: control, 5-FU (100 mg/kg), 5-FU+CHS (1 mg/kg), 5-FU+CHS (2 mg/kg) and CHS (2 mg/kg). 5-FU treatment was administered intraperitoneally (i.p.) on the first day and CHS (i.p.) were applied for the following 3 days. 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 spectrophotometric methods. MDA, TOS, 8-OHdG and IL-6 levels were significantly higher ($p<0.05$) and TAS and CAT levels level were significantly lower ($p<0.05$) in the 5-FU group than in the control group. CHS treatments significantly restored the levels of oxidative stress and inflammation parameters in a dose-dependent manner ($p<0.05$). Our results suggest that CHS can have a therapeutic effect against 5-FU-induced ovarian damage and therefore the use of CHS after chemotherapy may be beneficial in abolishing 5-FU-induced reproductive toxicity.

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

ÖZET

5-florourasil (5-FU), çeşitli maligniteleri tedavi etmek için etkili ve yaygın olarak kullanılan bir kemoterapötik ajandır, ancak doza bağlı doku toksisitesi nedeniyle terapötik kullanımı sınırlıdır. Birçok çalışma, çeşitli dokularda 5-FU'nun neden olduğu hasarın patogenezinde oksidatif stres ve inflamasyonun önemli bir rol oynadığını doğrulamıştır. Doğal bir flavon olan krisin (CHS), antioksidan, anti-inflamatuvar ve antikanser de dahil olmak üzere çeşitli faydalı aktiviteler sergileyebilmektedir. Bu çalışmanın amacı, sıçanların yumurtalık dokusunda 5-FU ile indüklenen oksidatif stres ve inflamasyona karşı CHS'nin terapötik etkisini ilk kez belirlemekti. Otuz adet dişi sıçan kontrol, 5-FU (100 mg/kg), 5-FU+CHS (1 mg/kg), 5-FU+CHS (2 mg/kg) ve CHS (2 mg/kg) olmak üzere 5 gruba ayrıldı. İlk gün intraperitoneal (i.p.) 5-FU tedavisi, takip eden 3 gün CHS (i.p.) uygulandı. 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 spektrofotometrik yöntemlerle belirlendi. 5-FU grubunda kontrol grubuna göre MDA, TOS, 8-OHdG ve IL-6 düzeyleri anlamlı olarak yüksek iken ($p<0,05$), TAS ve CAT düzeyleri ise istatistiksel olarak anlamlı düzeyde düşüktü ($p<0,05$). CHS tedavileri, oksidatif stres ve inflamasyon parametrelerinin seviyelerini doza bağlı bir şekilde istatistiksel olarak anlamlı derecede düzeltti ($p<0,05$). Sonuçlarımız, CHS'nin 5-FU ile indüklenen yumurtalık hasarına karşı terapötik bir etkiye sahip olabileceğini ve bu nedenle kemoterapiden sonra CHS kullanımının 5-FU ile indüklenen üreme toksisitesini ortadan kaldırmada faydalı olabileceğini düşündürmektedir.

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

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INTRODUCTION

Cancer is a disease characterized by the uncontrolled growth and proliferation of abnormal cells and an important public health problem worldwide.[1] Chemotherapy is one of the most widely used methods of cancer treatment.[2] 5-fluorouracil (5-FU) is a widely used antineoplastic agent in the treatment of breast, gastrointestinal, head and neck cancers. The anticancer effect of 5-FU is due its inhibition of thymidylate synthase enzyme, which is responsible for DNA and RNA synthesis in cancer cells.[3] However, 5-FU not only kills cancer cells, but also acts on rapidly dividing normal cells, causing side effects as with other chemotherapeutics.[4] Common intolerable and serious side effects of 5-FU-based chemotherapy are mucositis, hepatorenal toxicity, diarrhea, myelosuppression, cardiotoxicity, dermatitis and reproductive toxicity.[5] These toxic effects of 5-FU limit its clinical use.[4] Since 5-FU is generally used in combination with other chemotherapeutics, information about its harmful effects on the ovaries is limited.[6] However, experimental studies have revealed that 5-FU administration causes ovarian dysfunction, decreased reproductive hormones and follicle numbers in rodents in recent years.[6-8] 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.[9,10] It is therefore suggested that post-chemotherapy undesirable effects in the body can be eliminated by the treatment of chemopreventive agents with antioxidant and anti-inflammatory effects.[11]

Flavonoids are secondary metabolites found in natural products, especially plants, and are phytochemicals that have an important place in the human diet.[12] Chrysin (CHS, 5,7-dihydroxyflavone) is a phytochemical belonging to the flavonoid class, plants containing CHS has been used in traditional medicine since ancient times. CHS has been shown to be one of the main ingredients of some medicinal plants, fruits, mushrooms, honey and propolis.[13] CHS has wide variety of pharmacological activities, including antioxidant, anti-allergic, anti-asthmatic, anti-aging, antihypertensive, antimicrobial, hepatoprotective, neuroprotective, cardioprotective, renoprotective, anti-inflammatory, anticancer, anti-angiogenesis, antihyperlipidemic and antidiabetic.[14,15] There are increasing evidences that CHS reduce the toxicity of various chemotherapeutic agents, such as cyclophosphamide[2], cisplatin[16], 5-FU[17], methotrexate[18] and doxorubicin[19] in different tissues through its antioxidant and anti-inflammatory potential. 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 CHS on 5-FU-induced ovarian damage in an experimental rat model. The aim of this study was therefore to examine whether CHS has a therapeutic effect against 5-FU-induced ovotoxicity within the framework of oxidative stress and inflammation, for the first time.

METHODS

Chemicals

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

Animals

The thirty female Sprague-Dawley rats (150±15 g) were obtained from Surgical Practice Research Center of Karadeniz Technical University (Trabzon, Turkey). Rats were housed at room temperature (25°C) with 12 h light/dark cycles and free access to standard pellet diet and tap water. Animals received humane care in accordance with the guidelines of the US National Institutes of Health and prior permission was sought from the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol No: 2021/66). Before treatment, rats were allowed to acclimate for 7 days. 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.[20]

Experimental design

After the familiarization period, the rats were randomly divided into 5 groups with 6 animals in each group. The rats of Group I (control) received physiological saline in first day and DMSO for three consecutive days. The rats of Group II (5-FU) received 5-FU (100 mg/kg) in first day and DMSO for three consecutive days. The rats of Group III and IV (5-FU+CHS groups) received 5-FU

(100 mg/kg) in first day and CHS (1 and 2 mg/kg) for three consecutive days, respectively. The rats of Group V (CHS *per se*) received physiological saline in first day and CHS (2 mg/kg) for three consecutive days. 5-FU and CHS were dissolved in physiological saline and DMSO, respectively. All drugs were administered intraperitoneally (i.p.). Doses of 5-FU[21,22] and CHS[20,23] were selected based on previous 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.[24] 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.[25] 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[26]:

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

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

As shown in Table 1, there were significant increase in the levels of MDA, TOS, OSI, 8-OHdG and IL-6 in the 5-FU-treated group compared with the control group ($p=0.016$, $p=0.0001$, $p=0.0001$, $p=0.0001$ and $p=0.0001$, respectively). Treatment with CHS (1 mg/kg) decreased only the levels of TOS, OSI, 8-OHdG and IL-6 compared with only 5-FU-treated rats ($p=0.0001$, $p=0.0001$, $p=0.045$ and $p=0.002$, respectively). However, there were marked reductions in MDA, TOS, OSI, 8-OHdG and IL-6 levels in case of group treated with CHS (2 mg/kg) as compared to the only 5-FU-treated group ($p=0.033$, $p=0.0001$, $p=0.0001$, $p=0.0001$ and $p=0.0001$, respectively).

The TAS and CAT levels were significantly depleted in the 5-FU-treated group compared to the control group ($p=0.027$ and $p=0.001$, respectively). However, the TAS and CAT levels in the CHS (2 mg/kg)-treated group were significantly increased as compared to the only 5-FU-treated group ($p=0.033$ and $p=0.006$, respectively).

In additon, treatment with CHS (2 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. Comparison of the levels of biochemical parameters of all experimental groups

	Control	5-FU	5-FU+CHS (1 mg/kg)	5-FU+CHS (2 mg/kg)	CHS (2 mg/kg)
MDA (nmol/mg protein)	29.3±9.3	75.9±41.9[a]	45.3±23.4	33.5±17.9[b]	25.7±7.9
TOS (μM H_2O_2 equivalent/L)	10.8±1.6	58.3±14.1[a]	23.2±13.5[b]	11.1±1.7[b]	11.1±4.3
TAS (mM trolox equivalent/L)	0.93±0.37	0.30±0.13[a]	0.63±0.32	0.92±0.42[b]	0.95±0.39
OSI (arbitrary unit)	1.3±0.5	24.8±9.9[a]	3.8±1.0[b]	1.5±0.8[b]	1.3±0.6
8-OHdG (ng/mg protein)	20.5±19.4	100.9±27.2[a]	70.2±14.3[a,b]	22.6±12.5[b,c]	22.9±10.5
CAT (mIU/mg protein)	142.5±26.0	71.1±18.5[a]	109.1±25.0[a]	128.8±24.4	135.4±32.7
IL-6 (pg/mg protein)	111.8±33.1	432.4±155.7[a]	224.5±98.0[b]	117.9±21.7[b]	118.6±21.5

5-FU: 5-fluorouracil, CHS: chrysin, 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+CHS (1 mg/kg) group.

DISCUSSION

Ideal chemotherapy aims to cause minimal damage to healthy cells while killing cancerous cells. However, there is no chemotherapy protocol that does not harm healthy cells at all in practice.[6] 5-FU is one of the most widely used chemotherapeutics in the world, and ovarian tissue is one of the tissues most affected by 5-FU chemotherapy.[8] 5-FU-induced tissue toxicity is a complex and multistage phenomenon. It involves a number of pathological processes, such as overproduction of ROS, alteration of various signaling pathways and increased inflammation. It is therefore suggested that the use of agents with antioxidant and anti-inflammatory potential may be beneficial in eliminating 5-FU-related tissue toxicity.[5] This study therefore aimed to evaluate the therapeutic efficacy of CHS against 5-FU-induced ovarian damage 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.[11] MDA is a lipid peroxidation end product and accepted as a direct indicator of the degree of oxidative stress.[12] 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.[27] Oxidative stress also increases DNA damage and 8-OHdG is one of the main products of DNA oxidation.[28] The increased MDA, TOS, OSI and 8-OHdG levels and decreased TAS levels in 5-FU-treated rats indicates that 5-FU toxicity is mediated by ROS-induced oxidative cell damage. These findings are consistent with data from previous studies demonstrating that 5-FU increases oxidative stress and DNA damage.[4,5,10] CHS treatments restored these levels in a dose-dependent manner. The alleviation of oxidative stress and DNA damage parameters by CHS treatments with may be due to the free radical scavenging potential of CHS.[14,15] Similar with our results, CHS has previously been shown to prevent chemotherapeutic-induced tissue damage by inhibiting the levels of oxidative stress and DNA damage in experimental models.[11,16,18,19]

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.[12,20] CAT is the enzyme with the highest known turnover number and catalyzes the reduction of hydrogen peroxide to water.[28] The findings showed that systemic administration of 5-FU suppressed CAT levels 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.[11,29,30] However, treatments with CHS significantly increased the levels of CAT in a dose-dependent manner. Similarly, CHS has previously been shown to prevent chemotherapeutic-induced tissue damage by increasing the levels of antioxidant enzymes in various experimental models.[31-33]

Oxidative stress and inflammatory processes are closely related and pro-inflammatory cytokines play an important role in chemical-induced acute tissue

injury.[34] Increasing evidences point to the role of increased inflammation in 5-FU-induced tissue damage.[5,11,35] 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.[2,36] Our findings revealed that higher IL-6 levels appeared in the ovarian tissue of rats exposed only to 5-FU than control group and CHS treatments significantly reduced these values in a dose-dependent manner. This improvement appears to be due to the anti-inflammatory property of CHS, which has often been demonstrated.[14,15] Consistent with our results, CHS has previously been shown to prevent chemotherapeutic-induced tissue damage by inhibiting inflammation in experimental models.[2,32,33]

Flavonoids are secondary metabolites originating from natural products and it is suggested that regular and balanced intake of flavonoids is associated with a lower risk of cancer, neurodegenerative and cardiovascular diseases.[12] The antioxidant activities of flavonoids are due their ability to scavenge free radicals, chelate metal ions, and modulate antioxidant enzymes.[33] CHS is a popular member of the flavonoid family, and its antioxidant activity has been reported to be mainly due to the hydroxyl and keto groups in its rings.[37] Therefore, it is thought that the therapeutic effect of CHS on 5-FU-induced ovarian damage is mainly due to its antioxidant properties.

CONCLUSION

CHS could attenuate 5-FU-induced ovarian toxicity by decreasing oxidative stress and inflammation and increasing antioxidant status. This study supports the hypothesis that CHS is a potential therapeutic compound that can be used for the alleviation of 5-FU-induced ovarian injury.

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Authorship contribution statement

Consept and desing: EAD.

Acquisition of data: EAD, HK, SD and NTA

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

Drafting of the manuscript: EAD and 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: 2021/66) 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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