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The protective effects of silymarin in 5-fluorouracil-ınduced hepatotoxicity and nephrotoxicity in rats

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Abstract

Silymarin as an antioxidant compound has hepatic and renal protection effects. Numerous studies have reported liver and kidney damage caused by 5-fluorouracil (5-FU). Hence, the present study aimed to evaluate the protective effects of silymarin against 5-FU-induced hepatotoxicity and nephrotoxicity. Rats were divided into three groups: control (distilled water + dimethyl sulfoxide1ml/day intraperitoneal for two weeks), 5-FU (distilled water + dimethyl sulfoxide1ml/day intraperitoneal from the first day to the end of the eighth day along with 20mg/kg of 5-FU from the ninth to the end of the study), and 5-FU + silymarin (50mg/kg silymarin /day intraperitoneal for 2 weeks along with 20mg/kg of 5-FU from the ninth day to the fourteenth day). At the end of the experiment, the rats were killed and blood samples were taken for measuring serum alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, and antioxidant activities. Also, liver and kidney tissues were sampled. Results revealed that the activities of ALP, ALT, AST, and LDH in the 5-FU group were higher than in the control group, while their activities were similar in both silymarin and control groups. The silymarin group had a significant decrease (20.64%) in urea compared to the 5-FU group. Also, the silymarin group had significant increases (37.47%) in total antioxidant capacity compared to the 5-FU group. Histopathological analyses of the liver revealed the hepatic focal necrosis and renal epithelial necrosis in the 5-FU group compared to the control group. However, there were not notable pathologic changes to liver and kidney tissues of the silymarin group. It was concluded that silymarin had the protective effects on 5-FU-induced hepatotoxicity and nephrotoxicity.

Keywords: 5-Fluorouracil, Silymarin, Hepatotoxicity, Nephrotoxicity

Introduction

5-fluorouracil (5-FU) is an antimetabolite agent with an antineoplastic activity that can interrupt the synthesis of DNA and RNA in normal cells. It has been reported that the majority of 5-FU is eliminated by liver metabolism, and only its small portion is removed via kidney excretion. This analog is widely used in chemotherapy for treating several cancers such as colon, breast, head, neck, and pancreatic cancers (Longley et al., 2003) However, its use can lead to serious toxicity and unwanted side effects (Alvarez-Cabellos et al., 2007; Inoue et al., 2009). 5-FU has hepatotoxic effects along with increased activities of aspartate transaminase (AST), alkaline

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phosphatase (ALP), and lactate dehydrogenase (LDH) (Gelen et al., 2017; Ray et al., 2017). Some researchers suggested that 5-FU (similar to other chemotherapeutic agents) destroyed the liver, induced reactive oxygen species, and inhibited antioxidant defense mechanisms. Therefore, most studies focused on the use of antioxidants to prevent chemotherapy-induced hepatotoxicity (Behling et al., 2006). Also, 5-FU can be catalyzed into dihydrouracil, which is further catabolized to α-fluoro-β-alanine, ammonia, urea, and carbon dioxide in the liver, and subsequently induced renal toxicities (Yousef and Abolewafa, 2017; Rashid et al., 2014). In addition, several clinical trials have been conducted to investigate the effects of natural therapies to reduce the side effects of anti-cancer drugs (Matouk et al., 2013). Silymarin is a natural flavonoid extracted from milk thistle (*Silybum marianum L. Gaertn*.), which contains antioxidant properties and immunomodulatory, antifibrotic, antiproliferative, and antiviral effects (Loguerico et al., 2011). This compound maintains the integrity of the hepatocyte membrane and inhibits toxins entering the liver. Also, it can donate electrons to stabilize free radicals and reactive oxygen species (ROS) due to its phenolic nature. In addition, it has been reported that silymarin could prevent lipoperoxidation of cell membranes via affecting intracellular glutathione (Karimi et al., 2011). The hepatoprotective effects of silymarin have been confirmed in various studies. Silymarin improved acetaminophen-induced liver damage in hypertensive rats. In this study, Silymarin reduced histopathological changes and liver function tests including AST and ALT (Freitag et al., 2015). In a study in 2019, it was shown that silymarin was able to reduce the carbon tetrachloride induced liver damage at the histopathological level, which was accompanied by a decrease in the amount of malondialdehyde (MDA) (Baradaran et al., 2019). Guzel et al. (2019) demonstrated that silymarin, as an antioxidant compound, had protective effects against vancomycin-induced kidney damage in rats and was associated with significant reductions in serum BUN and creatinine. Also, Karimi et al. (2005) found that milk thistle seed extract had protective effects against cisplatin-induced acute nephrotoxicity in rats. According to the above studies, this study was conducted to evaluate the efficacy and protective effects of silymarin against 5-FU-induced hepatotoxicity and nephrotoxicity in rats.

Materials and Methods

Animals and experimental design

The present study was performed on 24 male (two-month-old) Sprague-Dawley rats with a weight range of 220-250 g. The studied rats were kept in controlled conditions in terms of ventilation, temperature, and humidity, a light/dark cycle of 12:12, and assured easy access to standard food (Javaneh Khorasan co., Iran) and water. In this study, animals were randomly divided into three groups (n=8 per group) as follows:

1. Control group. Animals were intraperitoneally (i.p.) administered with 1ml distilled water + dimethyl sulfoxide (DMSO, Merck, 0.2 ml) per day for two weeks.
2. 5-FU group. The animal was injected 1ml of distilled water + DMSO daily from the first day to the end of the study along with 20 mg/kg of 5-FU (i.p., Merck) from the ninth to the fourteenth day of the study. The interval between injections was 30 minutes (Gelen et al., 2018).
3. Silymarin (Sigma-Aldrich) + 5-FU group. Animals were injected 50 mg/kg (i.p.) silymarin per day for two weeks along with 20 mg/kg of 5-FU (i.p.) from the ninth to the fourteenth day of the study. The interval between injections was 30 minutes (Vangaveti et al., 2021).

At the end of the experiment (on the 15th day of the experiment), animals were anesthetized with the injection of ketamine (80 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). Next, all rats were sacrificed after collecting blood samples (cardiac puncture) to determine the biochemical and oxidative stress parameters. The liver and kidney tissue samples were then subjected to histopathological examinations.

Animal ethics

All animal of experiments were approved by the State Committee on Animal Ethics, Shiraz University, Shiraz, Iran (IACUC no: 4687/63). The recommendations of European Council Directive (86/609/EC) of November 24, 1986, regarding the standards in the protection of animals used for experimental purposes, were also followed.

Biochemical parameters

Blood tubes were centrifuged at 2500 rpm for 12 min to separate sera, and subsequently, biochemical parameters related to liver function, e.g., ALT, AST, ALP, and LDH, and renal function, namely urea and creatinine concentrations, were measured. Serum biochemical parameters was measured using commercial kits (Pars Azmoon Co., Tehran, Iran) with the auto-analyzer Alpha Classic AT++ (Sanjesh Co., Isfahan, Iran).

Histopathological evaluation

Representative tissue specimens of liver and kidneys were immediately fixed in 10% neutral buffered formalin and the fixative was changed after 24 hours and then, were dehydrated in a graded ethanol series, cleared in xylene, embedded in paraffin wax, sectioned in 5 µm thickness, stained with H&E (Neutron) and finally, examined by routine light microscope (Olympus, Japan). The photos were taken by camera (Olympus, EP1).

Measurement of oxidative stress parameters

Semi-frozen sera were first thawed at room temperature and then crushed by a crushing apparatus. Next, the samples were transferred into glass test tubes with a volume of 10ml and completely homogenized using an ultrasonic homogenizer. The samples were again transferred into microtubules to purify the tissue debris and centrifuged at 5000 rpm for 20 min. In the next step, upper aqueous phases were separated with a sampler and pooled into new microtubes. MDA and total antioxidant capacity (TAC) were quantified using commercial kits (ZellBio GmbH, Germany) as described by the manufacturer.

Statistical analyses

Statistical analysis and drawing of the figures were performed using GraphPad Prism v6.0 (GraphPad Software, USA). Statistical comparisons were performed using analysis of variance (ANOVA) followed by Tukey post hock test. All data were represented as mean ± standard error of the means (SEM); and $p<0.05$ was considered as significant.

Results

Biochemical tests

Liver function tests

ALP concentration in the 5-FU group was assessed equal to 536.8±83.72 IU/L (Table 1), which had a significant increase compared to ALP enzymatic activity of the control (299.8±40.9) and silymarin (280.8±38.67) groups.

Furthermore, ALT enzymatic activity in the control group was 67.19±4.92 IU/L and increased slightly to 74.25±9.71 IU/L under the application of 5-FU treatment. On the other hand, it was decreased equal to 66.69±6.20 under the administration of silymarin (Table 1). In other words, although the highest ALT enzymatic activity was recorded for samples treated with 5-FU, no significant differences were observed between the enzymatic activity of ALT of the studied groups. The AST

enzyme content in rats treated with 5-FU was assessed equal to 318.3±32.68 IU/L, which had a significant increase (p<0.01) compared to the content of AST enzyme of the control and silymarin groups with mean values of 177.9±27.09 and 173.6±15.3IU/L, respectively (Table 1). In addition to, the enzymatic activity of LDH for control, 5-FU, and silymarin groups were assessed equal to 2029±425, 3183±138, and 1832±318.7 IU/L, respectively. According to the evidence, it was observed a significant increase (p<0.05) in LDH enzyme content for the 5-FU group compared to the other two groups (Table1).

Table 1. The effects of silymarin on serum enzymatic activity in 5-fluorouracil-induced liver damage

Group	ALT IU/L	AST IU/L	ALP IU/L	LDH IU/L
Control	67.19±4.92	177.90±27.09	299.8±40.90	2029±425.4
5-FU	74.25±9.71	318.30±32.68**	536.8±8372*	3183±138.1*
5-FU+Silymarin	66.69±6.20	173.60±15.30	280.8±38.67	1832±318.7

The results were expressed as mean±SEM, n=8. *p<0.05 and **p<0.01 against other groups.

Kidney function tests

Serum urea concentrations of the experimental groups are shown in Figure 5. According to the results, it was observed that the urea concentration in the 5-FU group was equal to 55.13±3.53mg/dl, which had a significant increase (p<0.001) compared to the control group (38.75±2.14mg/dl). In contrast, the urea concentration for the silymarin group (43.75±1.44mg/dl) had a significant reductio (Figure 1A, p<0.05). The results of Figure 1B also showed that although the highest serum creatinine concentration was obtained under the application of the 5- FU treatment, there was no significant difference with other study groups. Based on the data, serum creatinine contents for the control, 5-FU, and silymarin groups were assessed equal to 0.85±0.02, 0.95±0.09, and 0.72±0.05 mg/dl, respectively.

Histopathological examination

Liver

Microscopically, the examination of the H&E-stained sections of liver tissue in the control group showed that the histological structure and architecture of the liver parenchyma was normal (hexagonal lobules), consisting of hepatocytes in the cellular plates arrangement with one or two large nuclei and eosinophilic cytoplasm. There was observed the central vein and portal triads (areas) in the central region of these hexagonal lobules and its periphery, respectively (Figure 2A). Also, mild vascular congestion and the presence of lymphocyte foci suggestive of extra medullary hematopoiesis were evident, especially around the vessels. In 5-FU treatment group, the liver parenchymal tissue had increased mild to moderate central vein congestion and sinusoidal dilatation (Figure 2B). In one case, there was a focus of hepatocellular degeneration and necrosis and the presence of mononuclear inflammatory cells on the necrotic area (Figure 2C). The presence of lymphatic centers related to hematopoiesis around the vessels was also evident. In the liver tissue of the rats treated with silymarin, only mild vascular congestion and the presence of hematopoietic lymphatic centers around the vessels were observed, similar to the control group (Figure 2D).

Kidney

Examination of H&E stained renal tissue sections in the control group showed

normalarchitecture of glomerular tuft and Bowman's capsule and renal tubular system (Figure 3A). Also, there was observed a slight presence of lymphocytes associated with hematopoietic centers. In the kidneys of 5- FU group, vascular congestion and the cytoplasmic degenerative changes were markedly increased (Figure 3B). Also, in one case, renal tubular epithelial cell degeneration and necrosis was observed without any infiltration of inflammatory cells (Figure 3C).

Histopathological examinations of the kidney tissue stained by H&E in the silymarin treatment group revealed that the structure and histological architecture of the kidney was similar to normal healthy control group (Figure 3D).

Antioxidant activity

TAC decreased in 5-FU-treated animals compared to the control group ($p<0.05$). However, TAC was significantly increased in the silymarin group in comparison to the 5-FU group ($p<0.05$) and was closer to the control group (Figure 4A).

The level of MDA in the 5-FU group was higher than the other groups but was not significant (Figure 4B).

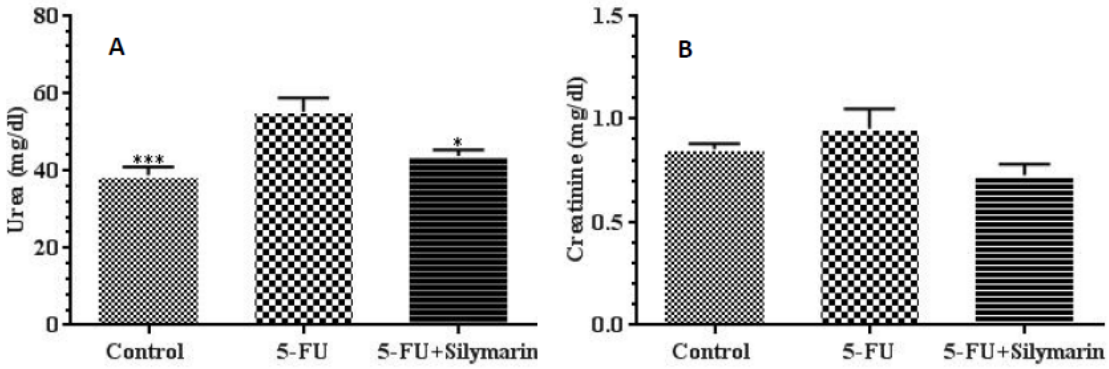

Figure 1.The effect of silymarin on serum urea (A) and creatinine (B) level in 5-fluorouracil (5-FU)-induced nephrotoxicity (n=8). The results were expressed as mean ± SEM (*p<0.05 and ***p<0.001 against 5-FU).

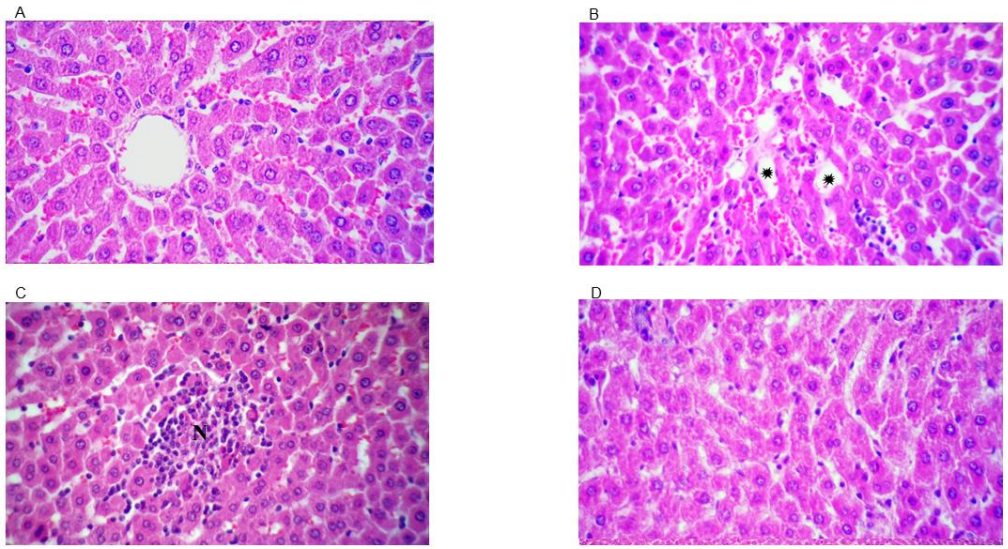

Figure 2. Histopathological evaluation of rat hepatic sections. control (A): normal histological structure of the liver parenchyma, 5-FU (B&C): mild to moderate sinusoidal congestion and dilatation (asterisks) & a focus of hepatocellular degeneration and necrosis (N), and 5-FU+sylimarin (D): normal histology of the liver parenchyma without any pathological lesions, H&E, X100.

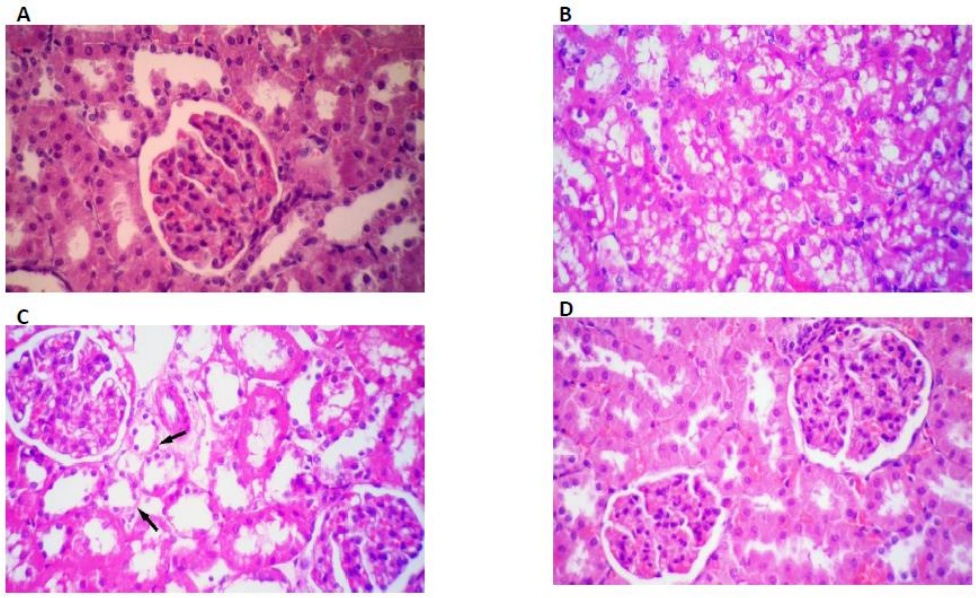

Figure 3. Histopathological evaluation of rat renal sections. control (A): normal histological structure and architecture of renal tubular epithelial cells and glomerular tuft, 5-FU (B&C): increased renal tubular epithelial cell degeneration and vacuole formation in the cytoplasm & acute tubular degeneration and necrosis (arrows), and 5-FU+sylimarin (D): normal structure of renal tissue including tubules, glomeruli, and interstitium without any pathological lesions, H&E, X100.

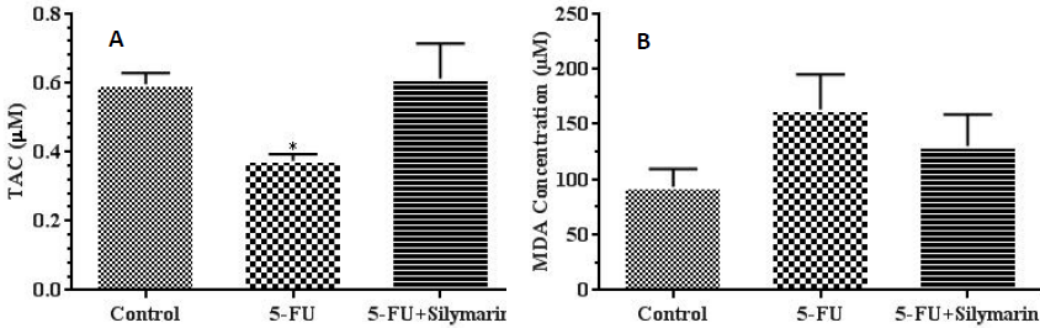

Figure 4.The effect of silymarin on serum total antioxidant activity (TAC) (A) and malondialdehyde (MDA) (B) in 5-fluorouracil (5-FU)-induced damage. The results were expressed as mean ± SEM (*p<0.05 against other groups).

Discussion

5-FU is the third leading chemotherapeutic agent in the treatment of solid cancers, including head and neck cancers and gastrointestinal tumors (boileve et al., 2020). However, like other chemotherapeutic agents, the use of 5-FU is associated with toxic effects (Inoue et al., 2009; Swamy et al., 2013) such as hepatotoxicity (Yaegashi et al., 2020), nephrotoxicity (Gelen et al., 2021), and cardiotoxicity (Sara et al., 2018). Based on the above, hepatotoxicity and nephrotoxicity induced by this factor can disrupt the cancer treatment process and prevent the completion of the therapy period.

In one study, Gelen et al. (2017) showed that administration of 5-FU was associated with a significant increase in AST, ALP, and LDH enzymatic activities and a decrease in GSH and GPx caused by oxidative damage (Gelen et al., 2017). In the present study, the use of 5-FU increased liver enzymatic activities, including ALP,

AST, LDH, and ALT. Malondialdehyde (MDA) was increased and decreased total antioxidant capacity (TAC), which was consistent with the results of the study performed by Gelen et al. (2017). In confirmation of the results of the present study and 5-FU-induced hepatotoxicity, Gelen et al. (2018) also found that administration of 5-FU increased enzymatic activities of ALP, AST, and LDH and decreased enzymatic activities of superoxide dismutase (SOD) and GSH (Gelen et al., 2018). In another study in 2019, silymarin decreased serum MDA and increased SOD in rats receiving acetaminophen, which indicates its antioxidant effect.According to the above researches, these findings can be attributed to ROS-induced oxidative stress (Abdulrazzaq et al., 2019).According to the above researches, these findings can be attributed to ROS-induced oxidative stress.

Wolf et al. (2013) investigated microscopic samples of liver tissue in patients receiving 5-FU and found that liver failures occurred in the form of steatosis, steatohepatitis, and sinusoidal obstruction (Wolf et al., 2013). Also, the histopathological results of the present study indicated focal necrosis of the hepatic parenchyma along with mononuclear inflammatory cells, congestion, and sinusoidal dilatation in the 5- FU-receiving rats.

Since the mechanism of 5- FU-induced liver damage, like many chemotherapeutic agents, appears due to increases in ROS and the inactivation of some body's antioxidant defense mechanisms, most studies have focused on the use of antioxidants towards preventing hepatotoxicity caused by the application of chemotherapy drugs (Behling et al., 2006; Pujari et al., 2021). Silymarin, natural flavonoid obtained from milk thistle, has immunomodulatory, antioxidant, anti-fibrotic, antiproliferative, and antiviral effects, which can maintain the hepatocyte membrane integrity and inhibit toxins entering the liver. Also, it was proved that silymarin could donate electrons to stabilize free radicals and ROS due to its phenolic nature (Karimi et al., 2011). Previous studies have shown that silymarin administration reduces the adverse effects of oxidative stress. In a study, the application of silymarin also reduced hepatic changes caused by the use of ribavirin (El-Abd, 2015).

Numerous studies have proven the antioxidant and anti-cancer properties of silymarin (Durak et al., 2005; Taleb et al., 2018). It was also suggested that some flavonolignans, such as silibinin, might enhance antioxidant activities and reduce lipid peroxidation (Rani et al., 2013). In one study, Mohamadifard and colleagues (2016) revealed that the use of silymarin significantly reduced MDA concentration and oxidative stress due to copper nanoparticles. A 2018 study showed that silymarin can reduce oxidative stress caused by cadmium chloride. In this study, the serum parameters of oxidative stress such as MDA decreased and SOD, catalase increased (Farjad and Momeni, 2018). In this regard, Davey et al. (2005) also showed that MDA is produced endogenously via lipid peroxidation.

In the present study, silymarin increased TAC and decreased MDA concentration. Accordingly, our findings may be due to the antioxidant properties of silymarin, which is consistent with the above researches. In addition to, taxifolin was introduced as the main component of antioxidant-rich of silymarin that reduced the adverse effects of free radicals in the study conducted by Anthony &Saleh (2013). In another study, Jouhari et al. (2018) found that the administration of silymarin in rats with endometritis was associated with increased levels of serum TAC during 21 days. Also, another study reported that silymarin decreased ROS and MDA concentrations and increased TAC in patients with thalassemia major (Darvishi-Khezri et al., 2017). In line with our findings, Gargari et al. (2015) also confirmed that silymarin

elevated antioxidant parameters, e.g., TAC, SOD, and GPX, in patients with type 2 diabetes mellitus.

Nephrotoxicity is one of the serious complications of using 5-FU in the treatment of cancer. Increased oxidative stress plays an important role in the pathogenesis of 5-FU-induced nephrotoxicity (liu et al., 2018). So far, no comprehensive studies have been reported on the effects of silymarin on reducing and preventing the adverse and toxic effects of 5-FU, as an anti-cancer chemotherapy drug, on renal parenchyma. The cellular protective effects of silymarin are dependent on its antioxidant properties and scavenging free radicals, which can prevent any abnormalities in the composition of lipids responsible for maintaining the membrane fluidity through direct reactions of cell membrane components (Pradhan and Girish, 2006). Numerous studies have identified silymarin as an interesting herbal drug and a potential protective agent due to its antioxidant, anti-inflammatory, anti-fibrotic, anti-viral, anti-cancer, and anti-apoptotic effects (Kummer et al., 2001; Gebhardt 2002; Osuchowski et al., 2004; Watson et al., 2006; Gazak et al., 2007; Saller et al., 2008; elmowfy et al., 2013). Accordingly, in the present study, silymarin was used as an influential antioxidant agent, and the results of biochemical, antioxidant, and histopathological tests of the present study confirmed its protective effects in inhibiting 5-FU-ınduced nephrotoxicity.

In the present study, biochemical examinations of serum samples showed increases in urea and creatinine contents of 5-FU group rats compared to the control group, which was significant only for urea content. In the present study, histopathological examination also showed an increase in vascular congestion, and acute necrosis of renal tubular epithelial cells (without the presence of inflammatory cells) in the 5-FU group compared to the control group. Our findings also determined that the activities of antioxidants were significantly reduced under the administration of 5-FU, which might be related to 5-FU-induced oxidative stresses. A similar study presented by Rashid et al. (2014) indicated that urea and creatinine levels, as measures of kidney function, were increased and antioxidant activities decreased under the application of 5-FU. In another study, Gelen and his colleagues (2021) showed that 5-FU has been led to pathological changes in the kidneys and has been increased serum urea and creatinine by increasing oxidative stress. Here, the use of silymarin in combination with the 5-FU group decreased urea and creatinine levels, which was significant only for the urea concentration. Also, silymarin increased TAC content and decreased MDA compared to the 5-FU group. Other similar studies have shown that the silymarin combination in rats exposed to renal failure resulted in decreasing urea, creatinine, and MDA concentrations and increasing the activity of superoxide dismutase and glutathione peroxidase in serum and tissue samples (Taleb et al., 2018). In general, the observations and findings of the present study verified that the combination of silymarin had protective effects due to antioxidant activities against kidney damage caused by the administration of 5-FU. Guzel et al. (2019) showed that silymarin was effective in improving vancomycin-induced kidney damage. In addition, other studies have confirmed that the silymarin has a protective effect against cisplatin-induced acute nephrotoxicity (Karimi et al., 2005). Furthermore, the silymarin administration was introduced as an effective clinical drug in inhibiting drug-induced nephrotoxicity (Shahbazi et al., 2012). Microscopic examinations of the present study also demonstrated that the use of silymarin improved renal histopathological lesions caused by the 5-FU administration, so that kidney tissue in this group was similar to that in the control group. In the meantime, this finding was in line with the results presented in the

previous studies. In general, it can be concluded that the silymarin has protective and immunomodulatory effects against 5-FU-induced nephrotoxicity.

In the present study, it was found that silymarin reduced liver and kidney damage caused by 5-FU and improved the antioxidant activity. In general, despite confirming the protective effects of silymarin against the studied disorders, further studies with a large sample size are needed to better understand its effects.

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Conflict of interest

No conflict of interest, financial or otherwise is declared by the authors.

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بررسی اثرات سیلیمارین در پیش‌گیری از سمیت کبدی و کلیوی ناشی از ۵-فلوئورواوراسیل در رت

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چکیده

گزارش‌هایی از آسیب کبدی و کلیوی ۵-فلوئورواوراسیل وجود دارد و بنابراین، در مطالعه‌ی حاضر اثرات حفاظتی سیلی‌مارین بر روی سمیت کبدی و کلیوی القایی با ۵-فلوئورواوراسیل بررسی شده است. ۲۴ سر رت در سه گروه قرار گرفتند. گروه کنترل روزانه ۱ سی‌سی حامل سیلی‌مارین را برای دو هفته دریافت کرد. گروه ۵-فلوئورواوراسیل، از روز اول تا پایان روز هشتم روزانه ۱ سی‌سی حامل سیلی‌مارین دریافت و از روز نهم تا چهاردهم مطالعه روزانه ۲۰mg/kg داروی ۵-فلوئورواوراسیل داخل‌صفاقی تجویز شد و در گروه سوم (درمان)، تجویز ۵-فلوئورواوراسیل مشابه گروه قبل، منتهی از روز اول تا روز چهاردهم سیلی‌مارین روزانه به میزان ۲۵mg/kg داخل‌صفاقی تزریق شد. در روز پانزدهم نمونه خون رت‌ها برای اندازه‌گیری فعالیت آنزیم‌های عملکرد کبد و کلیه و فعالیت آنتی‌اکسیدانی اخذ شد و همچنین بافت کبد و کلیه برای بررسی هیستوپاتولوژی جمع‌آوری شد. مقدار آنزیم‌های ALP، ALT، AST و LDH در گروه ۵-فلوئورواوراسیل نسبت به گروه کنترل بیشتر بود؛ در حالی که مقدار این آنزیم‌ها در گروه سیلی‌مارین مشابه گروه کنترل بود. اوره در گروه ۵-فلوئورواوراسیل نسبت به گروه کنترل بیشتر بود و در گروه‌های سیلی‌مارین و کنترل مشابه بود. ظرفیت تام آنتی‌اکسیدانی در گروه سیلی‌مارین مشابه با گروه کنترل و بالاتر از گروه ۵-فلوئورواوراسیل بود. در بررسی‌های هیستوپاتولوژیک کبد و کلیه به ترتیب کانون محدود نکروز سلول‌های کبدی همراه با حضور سلول‌های التهابی و نکروز حاد سلول‌های پوششی لوله‌های کلیه بدون حضور سلول‌های التهابی در گروه ۵-فلوئورواوراسیل مشاهده شد. بافت‌های کبد و کلیه رت‌های گروه سیلی‌مارین، هیچ‌گونه تغییر پاتولوژیک نداشت. مطالعه‌ی حاضر نشان داد که سیلی‌مارین اثر حفاظتی بر سمیت کبدی القایی ناشی از ۵-فلوئورواوراسیل دارد.

کلمات کلیدی: ۵-فلوئورواوراسیل، سمیت کبدی، سیلی‌مارین

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