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Evaluation of the Effect of *Capparis spinosa L.* on Cisplatin-Induced Liver Injury in Male Rats based on Persian Medicine

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ABSTRACT

Background & Objective: Cisplatin as a chemotherapy drug causes liver damage by increasing inflammation. Hepatoprotective agents with antioxidant properties can be useful for preventing this complication. Capparis spinosa, as a natural antioxidant source, can help to eliminate these productions. The purpose of this study was to determine the effect of two different doses of hydroalcoholic extract of Capparis seed on cisplatin-induced liver damages in rats.

Materials & Methods: Forty male rats were divided into five groups (the control group, Cis (cisplatin) group, 200 C/S (Capparis spinosa), Cis + 50 C/S, and Cis + 100 C/S). Biochemical and histopathological evaluations were made. At the end of the study, all animals were euthanized with a CO2 gradient. Statistical analyses were performed through Graph Pad Prism Statistics software 9.1.2. The level of significance was set at $p < 0.05$.

Results: Liver function tests, antioxidant and inflammatory markers and histopathological changes were evaluated. Significant changes in the pathology results were noticeable. Central vein, portal vein and bile duct diameter, thickness of the hepatic artery wall, and hepatic sinusoids were significantly increased in the Cis and 200 C/S-fed groups, compared to the controls, and also changes in favor of improvement were evident in the treatment groups, especially in the Cis + 100 C/S group compared to the Cis and 200 C/S groups.

Conclusion: Based on pathology results, treatment with C. spinosa seed extract may be helpful in preventing cisplatin hepatotoxicity.

Keywords: Drug-Induced Liver Injury, *Capparis spinosa* L., Cisplatin, Medicine, Persian

Introduction

At present, the main origin of acute liver disease is viral hepatitis, whilst alcohol and viral hepatitis are the foremost origins of chronic liver disease; however, in the future drug-induced liver injury (DILI) will be gradually identified as a reason for acute hepatitis (1). Cisplatin, one of the antineoplastic agents, is most broadly prescribed in the management of various cancers. The recurrence of the ailment and the creation of resistant tumors initially responsive to treatment, happen within18–24 months. For this purpose, the dosage required to prevail over this resistance can lead to intensive cytotoxicity in normal cells, as hepatotoxicity, nephrotoxicity, etc., which fundamentally confines the clinical benefit of cisplatin-based treatment. The mechanisms of hepatotoxicity with cisplatin are not entirely comprehended; the relation between oxidative stress and cisplatin toxicity has been confirmed in numerous empirical models. Numerous reports have involved free radicals and reactive oxygen species (ROS) in cisplatin toxicity, linked with an increment in lipid peroxidation (LPO), declined levels of protein- bound sulfhydryl groups and glutathione (2, 3). Therefore, it is very important to search for ways to elude the dose-restriction complications of cisplatin at its tumoricidal doses for safe clinical usage. Numerous studies have revealed that the usage of diverse anti-oxidants and anti-inflammatory agents is beneficial versus the harmful effects of cisplatin on the liver and kidney (2, 3). Persian Medicine (PM), as an alternative medicine, suggests many remedial strategies to cure liver diseases, ranging from lifestyle betterment to herbal treatment (4). *Capparis spinosa L.*, which is named "Kabbar", "Shapleh", "Lagay", etc., is a member of the Capparidaceae family (5, 6), and is bred plentifully in dry areas of Asia, particularly in the Mediterranean domain

(7, 8). Previous information has recommended that numerous portions of the caper (leaves, flower buds, fruits, roots, and bark) can be applied to cure several ailments, including liver disorders, diabetes, hypertension, rheumatism, headaches, and kidney disease. Phytochemical studies of this plants have revealed numerous bioactive combinations such as spermidine, rutin, quercetin, kaempferol, stigmasterol, tocopherols, carotenoids saccharides, glycosides, flavonoids, alkaloids, terpenoids, volatile oils, fatty acids, vitamin C, vitamin E, and steroids (5, 9, 10). From a nutritional perspective, C. spinosa berries, which contain the seeds, have protein, lipids, carbohydrates, dietary fibers, vitamin C, and phenolic combinations, as the most potent bio antioxidants in plants (11-14). However, according to our literature review, there is no study to assess the hepatoprotective effects of hydroalcoholic seed extract of *C. spinose* on drug- induced liver injury. In this study, we used cisplatin to induce liver damage in rats that can lead to cirrhosis; and evaluated the effects of *C. spinose* hydroalcoholic seed extract in different treatment methods and doses on liver function tests, inflammatory, and antioxidant markers, and especially quantitative changes of pathology markers.

Materials and Methods

C. spinosa hydroalcoholic seed extract preparation

Caper fruits were purchased, from -Pars Abad Moghan, Ardabil, Iran. Traditional medicine and material medical research center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, provided the herbarium code 3969. (15). Having been extracted from the cleaned fruits, the seeds were dried in the shade at 25 to 30° C. Five hundred grams of plant seeds were pulverized and thrown into a percolator, where they were combined with 70% ethanol in a tightly- sealed container for 3 days. To eliminate the solvent, the solution was passed through a filter and deposited inside the plates under the laboratory hood. This process was repeated three times, with the final stage substituting distilled water for the alcohol in the percolator containing the seed powder. The dried extract was collected inside the plates as the final work for each phase.

Animal study

Razi Vaccine and Serum Research Institute provided male Sprague-Dawley rats weighing 250 ± 20 grams. The rats were housed in a standard humidity (40-70 percent) environment with a 12-hour light-dark timer and thermal settings (22±2 °C) with free access to regular rat chow and water two days before the investigation. Use of animals and experimental procedures were approved by Zanjan University of Medical Sciences' ethics committee (IR.ZUMS.REC.1399.352). The ARRIVE guidelines were followed for all procedures. The rats were divided into 5 groups, each of which contained 8 rats. The control group (n=8) had unrestricted access to food and water but were denied cisplatin or *C. spinosa* seed extract. For toxicity testing, one group (n=8) received 200 mg/kg of *C. spinosa* seed extract diluted in distilled water twice daily through a nasogastric tube for two weeks (200 C/S). Liver injury was generated with a single intraperitoneal injection of Cis (7.5 mg/Kg) and confirmed by a liver histology assay (2, 3), then the animals (n=24) were divided into 3 distinct groups: two treatment groups received cisplatin on the first day then were fed on 50 mg/kg and 100 mg/kg of the *C. spinosa* seed extract dissolved in distilled water through a nasogastric tube twice daily for 2 weeks (Cis+ 50 C/S and Cis+100 C/S) and to the Cis group that received no treatment, only cisplatin was injected five days before the end of the study. One day after gavage of the last dose of the extract to the three group, the rats were sedated with a ketamine-xylazine cocktail (xylazine 10 mg/kg and ketamine 100 mg/kg) intraperitoneally prior to the test, and blood samples were taken from the retro orbital sinus into heparinized microtubes and allowed to stand minutes at 37° C. In a SiGmA 3-16K centrifuge, blood samples were spun at 1500 g for 20 minutes at 4° C, and the separated serum was kept at -70° C for final analysis. The liver tissues were swiftly extracted, and one section was immediately preserved in 10% phosphate buffered formaldehyde for histological and immunohistochemical tests. For biochemical analysis, another section of the liver was homogenized in lysis solution with protease and phosphatase inhibitor cocktails. All animals were euthanized by CO2 at the end of the trial.

Biochemical assessment

The spectrophotometry method (Pars Azmon Co. Kit, Tehran, Iran) and an autoanalyzer equipment type (**MINDRAY BS-200** analyzer (**MINDRAY**, Shenzhen, **China**)) were used to test the blood levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). The level of serum Gamma–Glutamyl Transferase (GGT) was determined using the Szasz technique. The BROMOCRESOL GREEN method was used to quantify albumin, the Diazotized Sulfanilic acid method was used to detect bilirubin-total, and the Lactate Dehydrogenase Activity Assay Kit was used to measure lactate dehydrogenase. Pars Azmoon kits were used to measure the Pt and Ptt tests (Tehran, Iran). Antioxidant indicators including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX), and malondialdehyde (MDA) activity were assessed using a calorimetrically enzymatic assay kit (ZellBio GmbH, Germany) in each gram of liver tissue. Furthermore, inflammatory markers such as interleukin-6 (IL-6) and IL-1 were measured in each gram of liver tissue using DuoSet ELISA (R & D Systems, Inc.) kits.

Liver histopathology

Histological investigation was performed using the hematoxylin and eosin (H&E) stain method. Parts of each animal's hepatic lobes were excised and fixed in a 10% formaldehyde buffer, as previously stated. Then, the samples were dehydrated in various grades of alcohol before being embedded in paraffin. Hematoxylin and eosin were used to stain sections of 5 mm thickness. The

image-portlab program was used to examine images obtained at 400 magnifications.

Statistical Analysis

Graph Pad Prism Statistics software 9.1.2 was used for statistical analysis. All data was presented as means and standard deviations. The significance level was chosen at p 0.05. The Kolmogorov Smirnov Test was used to ensure that the variables had a normal distribution. One-way analysis of variance and the Bonferroni post-hoc test were used to compare the groups.

Results

Biochemical markers

Results of serum AST, ALT, ALP, Alb, Total Bil, GGT, LDH, and results of PT, PTT are shown in Figure 1. Serum AST (p =0.001), ALP (p =0.036), GGT (p =0.0003), and LDH (p =0.023) were significantly different among the groups. Although many of the changes are not statistically significant, decreased Alb levels and increased PT, ALT, and LDH levels are obvious in the Cis group compared to the control group. However, AST, ALP and GGT serum levels were increased in the control group compared with the Cis group Also, we found a reduced Alb level and increased PT, PTT, ALT, AST, GGT, Total Bil, and LDH levels in the 200 C/S group. In response to treatment, we also had a relatively good response to treatment with 100 mg/kg *C. Spinosa* seed extract. For example, serum LDH levels were significantly increased in rats that had received Cis and had been treated with 100mg/kg of *C. spinosa* seed extract compared with the Cis group (p=0.024). However, there were no noticeable changes in the Cis + 50 C/S group.

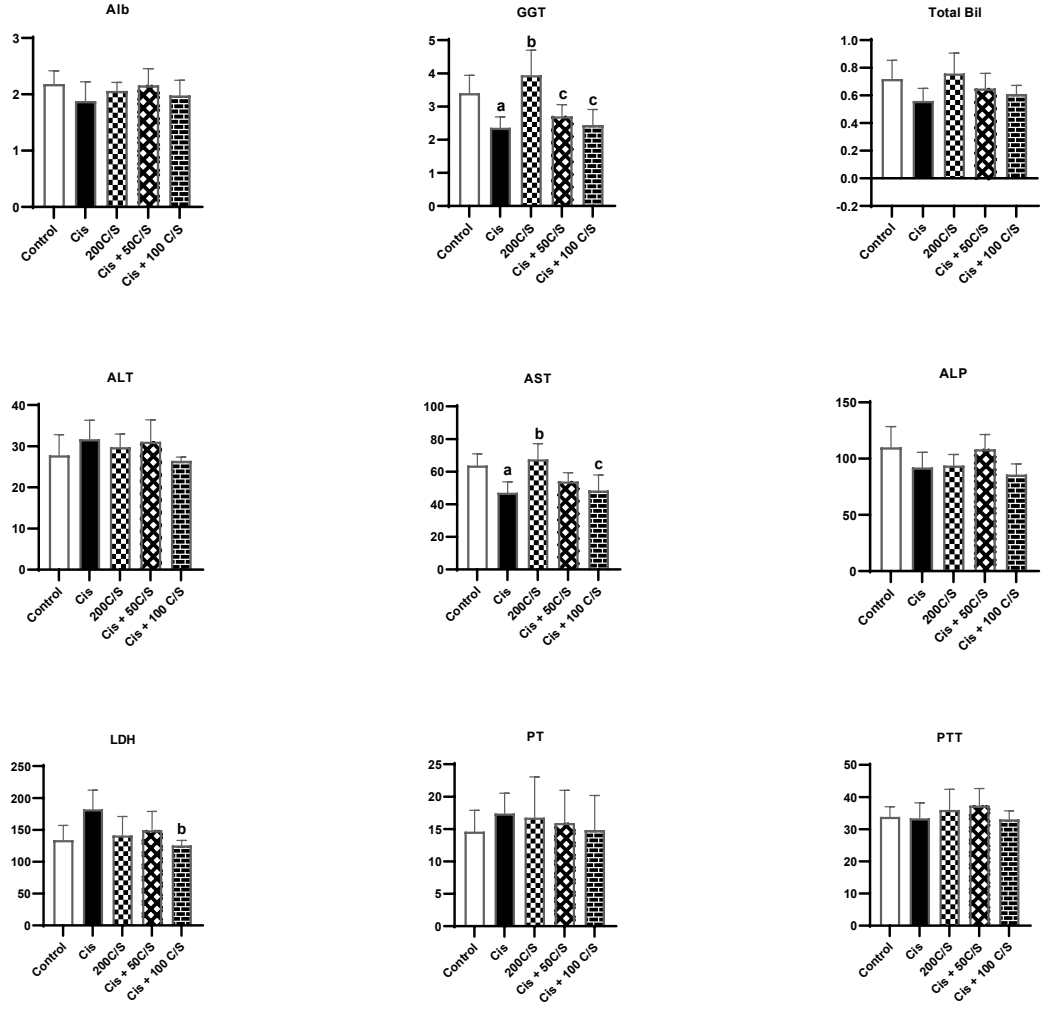

Figure 1. Biochemical parameters in the studied groups

Analysis was performed by ANOVA test followed by Bonferroni post-hoc analysis for intergroup comparisons.
a: Significantly different from the control group; b: Significantly different from the cis group; c: Significantly different from the 200C/S
Showing reduction of Alb level and elevation of PT, ALT, and LDH levels in the Cis group compared to the control group, Also, decrement of Alb level and increment of PT, PTT, ALT, AST, GGT, Total Bil, and LDH levels in the 200 C/S group compared to the control group and relatively good response to treatment with 100 mg/kg *C. Spinosa* seed extract compared with Cis group in Alb, ALT, ALP, PT, and PTT levels, and significant change in serum LDH level in the Cis+100C/S group compared with the Cis group

Liver inflammatory and antioxidant markers

As shown in Figures 2 and 3, tissue inflammatory and antioxidant levels were not statistically significant among the groups. However, we see an increase in MDA in the Cis and 200 C/S groups compared to the control and a decrease in the treatment groups. Among the antioxidant markers, we observed an increase in SOD and GPX in the 200 C/S group, as well as an increase in all three inflammatory markers – IL-6, IL-1β, and TNF-α – in the Cis and 200 C/S groups compared to the control group.

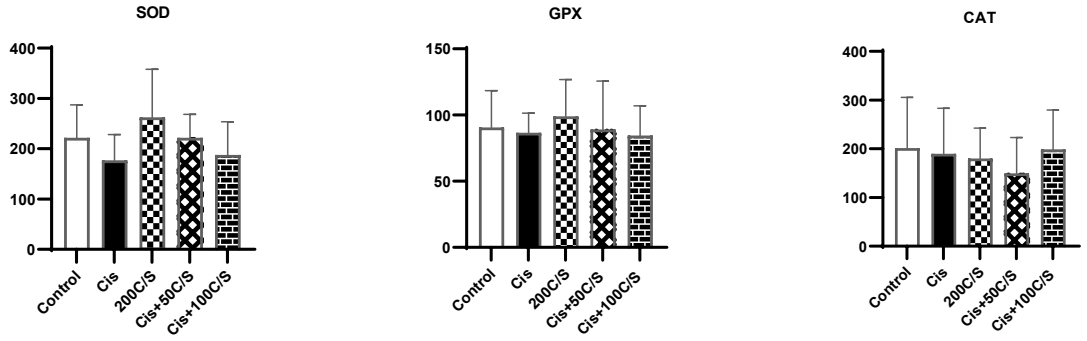

Figure 2. Tissue antioxidant parameters in the studied groups

Analysis was performed by ANOVA test followed by Bonferroni post-hoc analysis for intergroup comparisons
There is noticeable but insignificant changes in antioxidant markers such as reduction of SOD and GPX levels in the Cis group compared with control and relatively increment of these parameters in the C/S groups

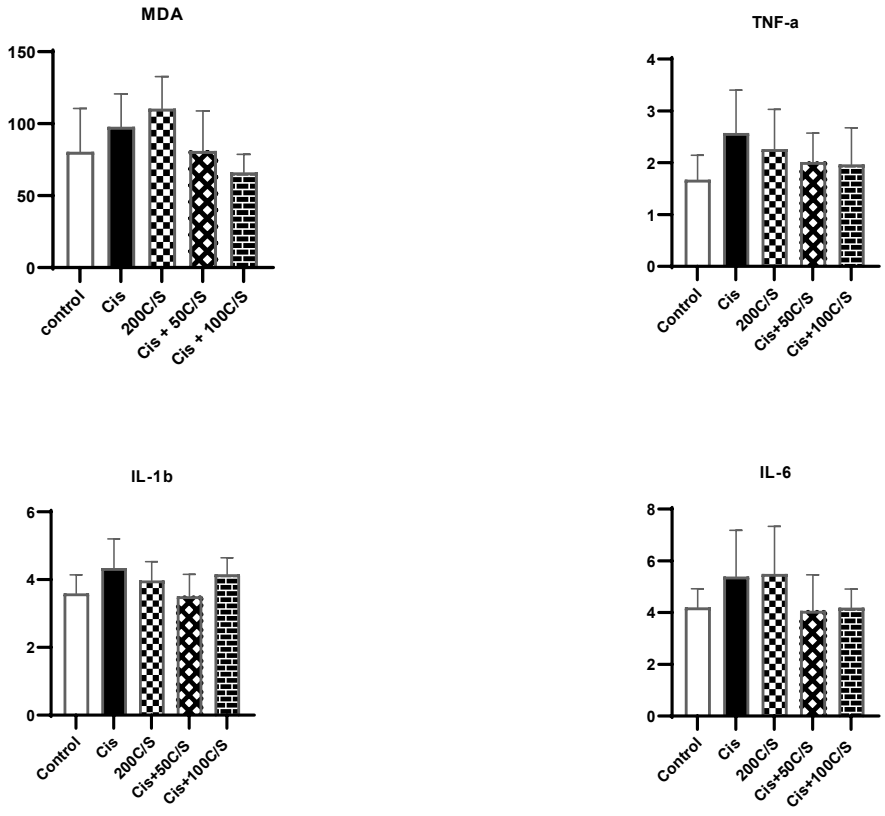

Figure 3. Tissue inflammatory parameters in the studied groups

Analysis was performed by ANOVA test followed by Bonferroni post-hoc analysis for intergroup comparisons
There is noticeable but insignificant changes in inflammatory markers such as elevation of all of them in the Cis and 200C/S groups compared with the control group and reduction in treatment groups

Histopathological assessment

Figures 4 and 5 show the histopathological graph of the liver in the studied groups. Results showed a significant difference in central vein diameter, portal vein diameter, thickness of the hepatic artery wall, bile duct diameter, and dilated hepatic sinusoids among the groups. Central vein's diameter was significantly increased in the Cis and 200 C/S-fed groups, compared to the controls ($p < 0.001$ and $p < 0.001$, respectively). However, daily intake of *C. spinosa* seed extract for two weeks decreased this diameter in the Cis+50 C/S and Cis+100 C/S groups compared with the Cis and 200 C/S groups ($p < 0.001$, $p < 0.001$, and $p < 0.001$, $p = 0.002$ respectively). Portal vein diameter was significantly elevated in the Cis and 200C/S groups, compared to the controls ($p < 0.001$ and $p < 0.001$, respectively). Also, the portal vein diameter was reduced in the Cis + 100 C/S-fed group compared to the Cis-one ($p = 0.024$). Hepatic artery wall thickness was significantly different among the groups ($p = 0.001$). Intergroup analysis indicated that the artery wall thickness was significantly increased in the Cis and 200C/S groups, compared to the controls ($p = 0.015$ and $p = 0.004$, respectively). Consumption of 100 mg/kg of *C. spinosa* seed extract for two weeks decreased artery thickness significantly compared to the Cis group ($p = 0.041$). Moreover, intake of 50 and 100 mg/kg of *C. spinosa* seed extract for two weeks improved arterial wall thickness compared to the 200C/S-fed group ($p = 0.036$ and $p = 0.010$, respectively). The bile duct diameter was remarkably elevated in the Cis and 200C/S-fed groups compared to the controls ($p < 0.001$, $p = 0.004$ respectively). Also, the bile duct diameter was reduced in the Cis + 100 C/S-fed group compared to the Cis-one ($p = 0.008$). Dilated hepatic sinusoids was increased in the Cis and 200C/S-fed groups compared to the controls ($p < 0.001$ and $p < 0.001$, respectively). However, the changes in the treatment groups were not significant compared to the Cis and 200 C/S groups, although a decrease was evident.

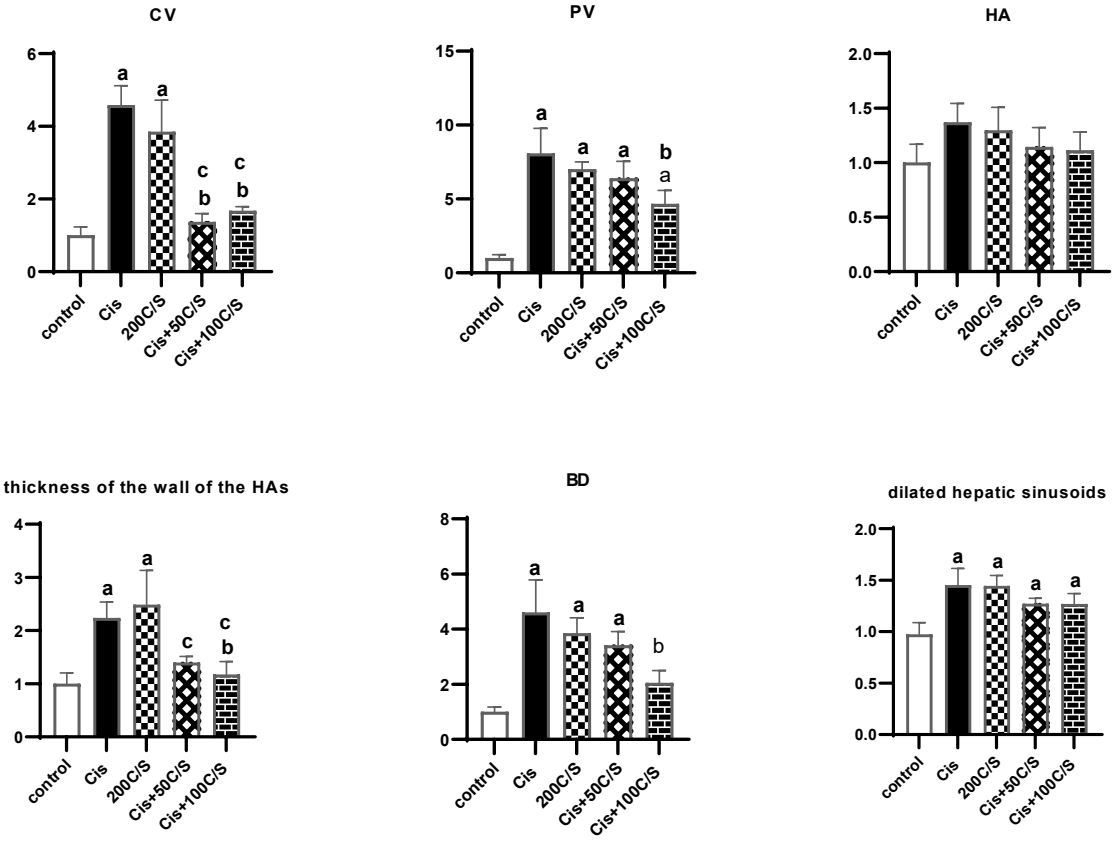

Figure 4. Pathological changes in the liver tissues of studied groups

Analysis was performed by ANOVA test followed by Bonferroni post-hoc analysis for intergroup comparisons.
a: Significantly different from the control group; b: Significantly different from the cis group; c: Significantly different from the 200C/S.
There is significant changes (increase) in almost all of the pathology markers in the Cis and 200C/S group compared to the control group, and changes in favor of improvement in the treatment groups, especially in the Cis + 100 C/S group compared to the Cis and 200 C/S groups in many of markers

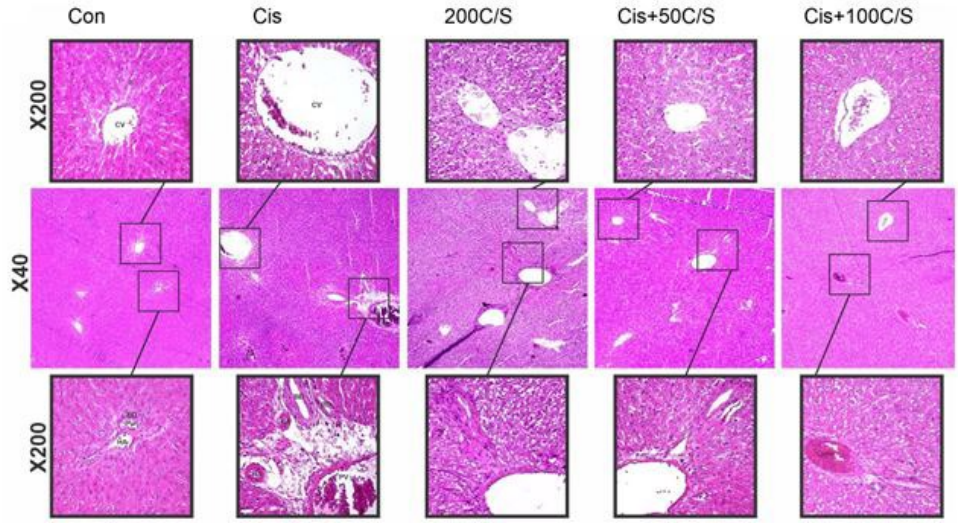

Figure 5. Photo micrograph of rat liver tissues by H&E staining

There is dilatation and congestion of the central vein and variable degenerative changes in the hepatocytes, dilatation and congestion of the portal vein, thickening of the wall of the hepatic artery, and dilated hepatic sinusoid in the Cis and 200C/S group, and evident improvement of the liver structure and normalization of the hepatocytes, sinusoids and portal area in the treatment group.

Discussion

Liver damage is a common complication following chemotherapy drugs, and different treatment methods are recommended to improve this complication. In the present study, we assessed the therapeutic effect of *C. spinosa* in two doses for two weeks on cisplatin-induced liver damage. According to the mentioned results, we had fewer significant changes in serum elements. For instance, reduced Alb levels and elevated PT, ALT, and LDH levels were obvious in the Cis group compared to the control group. These findings were consistent with other similar studies **(2, 3, 14, 16)**, which pointed out that such changes are expected when cisplatin is administered to rats. However, serum AST, ALT and GGT levels were not elevated in the Cis group. To our knowledge, ALT is more susceptible to acute liver harm, whereas AST is more susceptible to chronic harm **(16)**. On the other hand, Omar et al., indicated that the obvious changes in the enzymes act that result from cisplatin are owing to their leak from hepatocytes, which could be a secondary incident in the liver harm via cisplatin **(3)**. If the tests had been performed following the cisplatin injection, perhaps an increase in these serum indicators would have been visible. Also, we had a reduction in Alb level and a rise in PT, PTT, ALT, AST, GGT, Total Bil, and LDH levels in the 200 C/S group, which may show the hepatotoxic properties of *C. spinosa* in high doses; and these findings were in agreement with Fanoudi et al. findings **(17)**. Similar to other studies, we also had significant as well as non-significant changes in serum markers in the treatment groups **(14)**. Most of the improved changes were evident in the Cis + 100 C/S group. For example, serum LDH levels were significantly decreased in the Cis + 100 C/S group compared to the Cis-one ($p = 0.023$). Among tissue inflammatory and antioxidant markers, there were acceptable but non-significant results that were somewhat consistent with similar studies **(14, 18)**. However, we had significant changes in pathology results. Of all the items measured as pathology results, central vein diameter, portal vein diameter, thickness of the hepatic artery wall, bile duct diameter, and hepatic sinusoids were significantly increased in the Cis and 200 C/S-fed groups, compared to the controls, indicating similar results in limited studies **(2, 3, 16)**. In all of the above cases, we had changes in favor of improvement in the treatment groups, especially in the Cis + 100 C/S group compared to the Cis and 200 C/S groups. Hence, according to the present study and similar studies, cisplatin causes an obvious effect on the liver structures and functions. Cisplatin remarkably characterized hepatotoxicity in rats, specialized by considerable increases in serum ALT and AST, and this increase is allied with necrosis and lipid accumulation of hepatocytes. Cisplatin toxicity is recognized with augmented free radical generation and reduced anti-oxidant protection mechanisms. The induction of inflammatory reactions is another toxic effect of cisplatin prescription, which may be associated with oxidative stress that has an important pathogenic role in tissue harm. Significant histological changes in the liver tissues occurred in the cisplatin group, including congestion, dilatation, epithelial vacuolization, and mononuclear cell infiltration. There was congestion and dilatation in the central vein and the hepatic sinusoids with disjunction of the endothelial coating of the central vein. Also, dilated congested portal vein with epithelial hyperplasia of the bile duct and thickening of the hepatic artery wall and acidophilic exudate is obvious **(2, 3, 16)**. Because of these toxic effects of cisplatin, it is often not possible to increase the dose for higher efficacy. Various studies have

shown that the usage of various anti-oxidants and anti-inflammatory agents is efficient versus toxic effects of cisplatin on liver and kidney (2, 3). Medicinal plants have a significant role in healthcare systems all over the world due to their confirmed and efficient remedial traits (19). Truly, liver damage has become one of the most serious health worries, and the accessible synthetic medications (interferon and corticosteroids) are costly and may produce further injury (20). Herbal medicine, as a possible remedy, can prevent liver problems due to its safety, facile accessibility, affordability, and friendship with the environment (19). Many studies have indicated that natural biomolecules, containing phenolic compounds, carotenoids, and polysaccharides, are effective in hindering reactive oxygen species in organ pathologies. In addition, natural antioxidants are preferred to synthetic molecules due to their safe natural resources (20). Natural antioxidants in C. spinosa can purify damaging free radicals from our body (12). The risk of chronic diseases or disease progression may be decreased by increasing the body's natural antioxidant or taking dietary antioxidant supplements (12). One of the most substantial overall traits of Caper in Persian Medicine is its antitoxic (as named Teriaq) trait, which may be consistent with the antioxidant effects (6). On the other hand, Caper processed with vinegar can be efficient in resolving liver obstruction, particularly if consumed with a little olive oil just before mealtimes (6, 15). In a new study similar to the present study, Good nephroprotective effects were seen in treatment with CSEE (21). Also, in another study similar to the present study, Tir et al., detected the hepatoprotective and nephroprotective effects of *Capparis spinosa* seed extracts (CSSE), and their primary phytochemical screening specified that CSSE included a high content of phenolic combinations with high hepatoprotective and nephroprotective function (14). Also, in another study with the objective of assessing the anti-inflammatory and hepatoprotective effects of methanolic extracts from fruits and leaves of Capparis spinosa, Aichour et al., showed that *C. spinosa* leaf extract (CSLE) and fruit extract (CSFE) have anti-inflammatory and hepatoprotective effects, with a higher effect for the leaf extract (22). On the other hand, another study discovered that hydroalcoholic extract of Capparis spinosa root bark exhibited hepatoprotective effects on mice with liver injury due to CCL4 (23). Kalantari et al. reported that *C. spinosa* and quercetin are efficient in the prohibition of liver injury by t-BHP induction in mice (18). In addition, in a small randomized clinical trial, Khavasi et al., found the favorable effects of daily consumption of *C. spinosa* fruit pickle on liver enzyme tests (24). Also, in a number of studies, the effects of *C. spinosa* on other diseases have been confirmed. For example, *C. spinosa* downregulated inflammatory genes in patients with Alzheimer's disease (25). Eddouks et al., detected that the antihyperglycemic effect of *C. spinosa* may be associated with the avoidance of basal endogenous glucose genesis and the amelioration of insulin sensitivity in multi low dose streptozotocin-induced (MLDS) diabetic mice (26). In a similar study, Rahmani et al. found a remarkable decrease in blood sugar as well as a substantial reduction in blood triglycerides in diabetic rats following Caper fruit extract consumption (27). In another animal study, capers extract could promote mending mouth ulcers in rats by augmentation of the epithelium papillae thickness, declining the thickness of the mucus lining, increment of the number of blood vessels, and mast cells, and lessening of nitric oxide synthases (INOS) expression (28). To our knowledge, this is the first study to evaluate the effect and determine the best dose of *C. spinosa* seed extract on liver enzymes, inflammatory and antioxidant markers with a histopathological view in cirrhosis.

Conclusion

Liver damage following cisplatin injection with significant pathological changes is evident. Based on this study the *C. spinosa* seed extract in two different doses (50 and 100 mg/kg) had a good therapeutic effect on these cisplatin-induced changes. Therefore, *C. spinosa* seed extract may be of help to avoid the liver damage due to cisplatin chemotherapy. In future studies, by increasing the intervals between cisplatin administration and the final experiments, as well as measuring the level of tissue proteins by western blotting, it may be possible to obtain accurate results in order to generalize them to the human population.

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Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

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