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Research Paper

Beneficial Effects of Propofol and Silymarin on the Liver: Silymarin Lowers the Hyperlipidemia Induced by Propofol

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ABSTRACT

Background: Silymarin is utilized in the treatment of liver conditions primarily because of its antioxidant properties and its ability to lower blood lipid levels. Propofol, an anesthetic and antioxidant, is harmful to patients with hyperlipidemia. The aim of this study was to investigate the beneficial effects of silymarin and propofol on liver enzymes and blood indices. We also studied the impacts of propofol and silymarin on propofol-induced hyperlipidemia in male Wistar rats.

Methods: The rats were divided into four groups: 1) controls; 2) silymarin; 3) propofol; and, 4) combined propofol and silymarin. On the 22nd day after the treatments, all rats were anesthetized, and their blood samples were collected to estimate the levels of AST, ALT, ALP, LDH, TG, TC, LDL-C, and HDL-C. After being sacrificed, the liver was removed from each rat to determine the levels of MDA, GPx, GSH, and CAT. Moreover, histopathological examinations were performed on all liver samples.

Results: Silymarin and propofol, used either separately or in combination, had a favorable effect on the indicators of oxidative stress and the liver's antioxidant markers. The propofol treatment alone significantly increased the blood lipid parameters. The administration of Silymarin had a modulating effect on propofol-induced hyperlipidemia in rats.

Conclusion: Propofol and silymarin had favorable effects on the liver; however, propofol increased the blood lipids due to its lipid structure, which is a warning for patients with hyperlipidemia. In this regard, silymarin may be considered a protective option, making it a potential treatment for patients experiencing hyperlipidemia induced by propofol.

Keywords: Hyperlipidemia; Liver antioxidant factors; Liver enzymes; Male Wistar rats; Propofol; Silymarin

Introduction

Propofol (2,6-di-isopropylphenol) is a commonly used intravenous anesthetic agent and is an alkyl phenol formulation in a lipid emulsion [1, 2], with the empirical formula of $C_{12}H_{18}O$ [3, 4]. The soybean oil in the propofol emulsion is a mixture of neutral triglycerides containing unsaturated fatty acids. Among the propofol constituents, there are 9% glycerol, 85% triglycerides, and 7% phospholipids, meaning that 1 ml of propofol contains approximately 0.1 g fat [5]. Therefore, hyperlipidemia is one of the undesirable effects of propofol administration that is likely to occur during the hospital sedations of patients [6, 7].

Propofol is a strong intravenous hypnotic drug and a desirable anesthetic agent in recent decades because of its very few side effects plus immediate efficacy [8, 9]. This drug, similar to many other anesthetics, is an agonist of the gamma-aminobutyric acid receptors [10, 11]. Rapid induction, short half-life, and low incidence of postoperative nausea and vomiting make it a popular and widely used hypnotic agent [12, 13]. Some studies, in laboratory settings through various tests, have confirmed the antioxidant activity of propofol, including 1,1-diphenyl-2-picrylhydrazyl (DPPH free radical inhibition), hydrogen peroxide inhibition, metal chelation, superoxide anion radical inhibition, and total antioxidant activities. The results of these tests have shown that propofol can prevent lipid peroxidation and free radical chain reactions [14, 15].

Silymarin, a flavonolignan derived from *Silybum marianum*, is consumed because of its excellent hepatoprotective properties. It is a composition of three flavonolignans, including silybin, silychristine, and silidianin [16-18]. Silymarin has been used to treat hepatitis and other liver conditions induced by toxins, viruses, alcohol consumption, and liver cirrhosis [19, 20]. The most important aspects of its mechanism of

action include antioxidant activity and increased glutathione regeneration that enhances its concentration in the liver. Its other beneficial properties involve the blockage of toxins binding to receptors on cell membranes and excitation of ribosomal RNA polymerase following protein synthesis, leading to enhanced repair of the liver hepatocytes [21, 22].

Aim of the Study: This study aimed to investigate the effect of silymarin on the complications of hyperlipidemia caused by propofol and to examine the effect of either separate or concurrent administration of silymarin and propofol on the liver factors.

Materials and Methods

Silymarin was purchased from Sigma Chemical Co. (St Louis, MO, USA), and propofol was obtained from Tehran Chemie Pharmaceutical Co. (M.L. No: G/28/1156). All chemicals used in this study were of high analytical grades.

Animals: 14-week-old adult male Wistar rats, weighing 210 ± 10 g, were used in this study. The rats were housed in the laboratory under 12-hour light/dark cycles and controlled humidity (50%±5) and temperature (25±2°C). The animal care protocol was approved by the Institutional Animal Ethics Committee (Registration ID#: IR.DUMS.REC.1398.047; Proposal No. 1687: dated 06.01.2020) at Dezful University of Medical Sciences, Dezful, Iran.

Experimental Design: Animals were assigned to one of four groups (n=5) as follows:

1) Control group received distilled water by gavage for 21 days;

2) Silymarin group was given silymarin by gavage at 100 mg/kg every other day for 21 days [23];

3) Propofol group received propofol intraperitoneally (IP) at 4 mg/kg every other day for 21 days [24];

4) Combined propofol-silymarin group received silymarin by gavage at 100 mg/kg and propofol IP at 4 mg/kg every other day for 21 days.

All animals were anesthetized IP by ketamine (87.5 mg/kg) or xylazine (12.5 mg/kg) on the 22nd day of the study. Blood samples were collected from the heart in heparinized vials to estimate biochemical parameters using the specific diagnostic kits from the suppliers. The biochemical parameters included aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, triglyceride (TG), cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Liver tissue samples dissected from the rats were frozen at -70°C until later homogenization and analyses of the following biochemical parameters: malondialdehyde (MDA), glutathione peroxidase (GPx), glutathione (GSH), and catalase (CAT). Separate pieces of liver tissues from each rat group were kept in 10% formalin for later histopathological examinations.

Investigations of Biochemical Parameters: Phosphate-buffered saline was added to the homogenized liver tissue samples, which were then centrifuged at 12,000 rpm for 15 min at 4°C. Following that, the GSH, MDA, CAT, and GPx levels were measured in the supernatants. Moreover, the MDA contents of the liver tissue samples were evaluated based on the Thiobarbituric acid method [25]. The absorption of the samples was also read at 532 nm on a Hitachi's U-2000 double-beam UV/Vis spectrophotometer. The GSH levels of the tissue samples were measured according to an established method [26]. Further, the GPx activity of the samples was evaluated using the method proposed by Rotruck *et al.* [27].

Briefly, hydrogen peroxide (H_2O_2) and tert-butyl hydroperoxide were mixed with the tissue samples, and the absorption was read at 420 nm on an enzyme-linked immunosorbent assay reader [27-29]. For the CAT assay, potassium phosphate buffer (0.7 ml, pH: 7.0), hydrogen peroxide (0.1 ml), and a homogenized liver sample (100 µl) were mixed, and the absorption was read at 240 nm on the same spectrophotometer [29, 30].

Histopathological Examinations: Before performing the histopathological examinations, the liver tissue samples were washed in ice-cold physiological saline solution and fixed in 10% buffered formalin for 72 h. After paraffin wax embedding, the tissue samples were sectioned at 4-5µm thickness on a rotary microtome. The sections were stained with hematoxylin and eosin (H&E) dyes and examined at magnifications of 40x and 100x under a light microscope (Olympus BX 52; Tokyo, Japan) [31]. The percentage of structural damages was measured and scored semi-quantitatively as follows: 0 point: normal; 1 point: <10%; 2 points: 10-25%; 3 points: 26-75%; and 4 points: >75% damages. Finally, the percent damages were averaged for each measure [32].

Statistical Analyses: The study data were analyzed using Shapiro-Wilk's test to determine normality. Normal parameters were also evaluated by one-way analysis of variance (ANOVA). If the differences among the groups were significant, Tukey's multiple comparison post-test was also used, and the data were expressed as means ± standard deviations. The statistical analyses were performed on Graph Pad Prism software (version 8). A *P*-value of ≤0.05 was considered statistically significant.

Results

Effect of silymarin and propofol on liver enzymes: The effects of silymarin were observed based on the increased levels of liver enzymes in the serum. As shown in Figure 1, these included significant changes in the serum levels of ALT, ALP, and LDH. However, there was no significant change in the AST level. Moreover, the administration of propofol caused a significant increase in ALT; however, the rises in the

AST, ALP, and LDH levels were not significant. Regarding ALT, ALP, and LDH enzymes, the biochemical analyses showed that the administration of silymarin combined with propofol caused a significant increase in the serum enzymes compared to those found for the control group. However, no significant difference was found in the AST level (Figure 1).

Effects of silymarin and propofol on the liver lipid peroxidation: The lipid peroxidation was assessed based on the thiobarbituric acid reactive substances that were expressed as MDA levels. The MDA level significantly decreased in the liver samples of the silymarin group compared to that of the controls ($P \leq 0.05$). Furthermore, the level of MDA was reduced after treatment with propofol compared to that of the control group ($P<0.05$; Figure 2). The study data showed favorable effects of propofol and silymarin on the MDA levels of the liver samples, either used separately or combined.

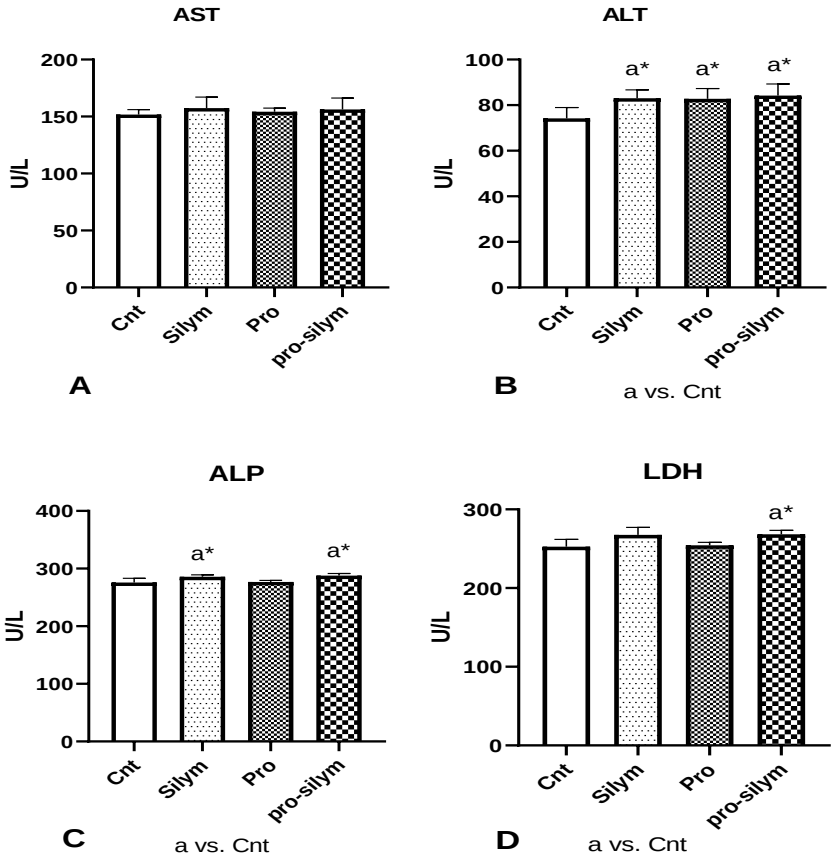

Figure 1: Effects of propofol and silymarin on (A) AST, (B) ALT, (C) ALP, and (D) LDH. The administration of propofol (4 mg/kg, intraperitoneally) and silymarin (100 mg/kg, gavage) every other day for 21 days, separately and together, were measured on enzymes. Values are expressed as mean ± SD (n=5). *$P<0.05$ and **$P<0.01$.

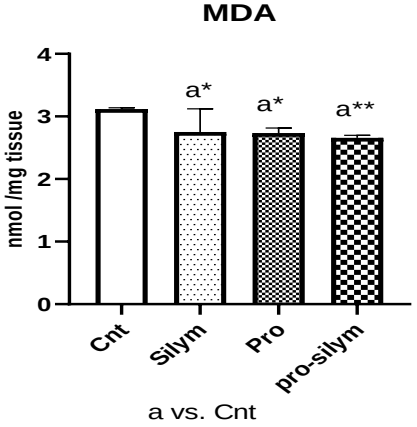

Figure 2: Effects of propofol and silymarin on lipid peroxidation of liver tissue. Rats received silymarin and propofol, as described in Figure 1. The values are expressed as mean ± SD (n=5). The results show that propofol and silymarin, separately and together, have the desired effects on lipid peroxidation. *$P<0.05$ and **$P<0.01$.

Effects of propofol and silymarin on antioxidant parameters of liver tissue: To determine the effect of silymarin and propofol alone or combined, we investigated the enzymatic and non-enzymatic antioxidant defense parameters. The effects of propofol and silymarin treatments were tested on the liver tissue antioxidants. These included GSH, GPx, and CAT, as presented in Figure 3. Compared to the control group, the silymarin treatment significantly increased the GSH, GPx, and CAT in the liver tissue samples. The propofol treatment boosted the GSH, GPx, and CAT in the same samples (P<0.05). The study data on GSH, GPx, and CAT levels showed favorable synergistic effects after silymarin and propofol were used in combination.

Effects of silymarin and propofol, separately or combined, on the total bilirubin and lipid factors: The effects of propofol and silymarin used separately or combined were evaluated on the lipid factors. These included TG, TC, LDL-C, HDL-C, and bilirubin. The propofol treatment increased the levels of TG, TC, and LDL-C as compared to those of the control group. The administration of silymarin alone or combined with propofol significantly reduced TG, TC, and LDL-C compared to the propofol treatment alone (Figures 4A, B & D). The HDL-C level decreased significantly in the propofol group but increased significantly in the silymarin group compared to those found in the controls (Figure 4D).

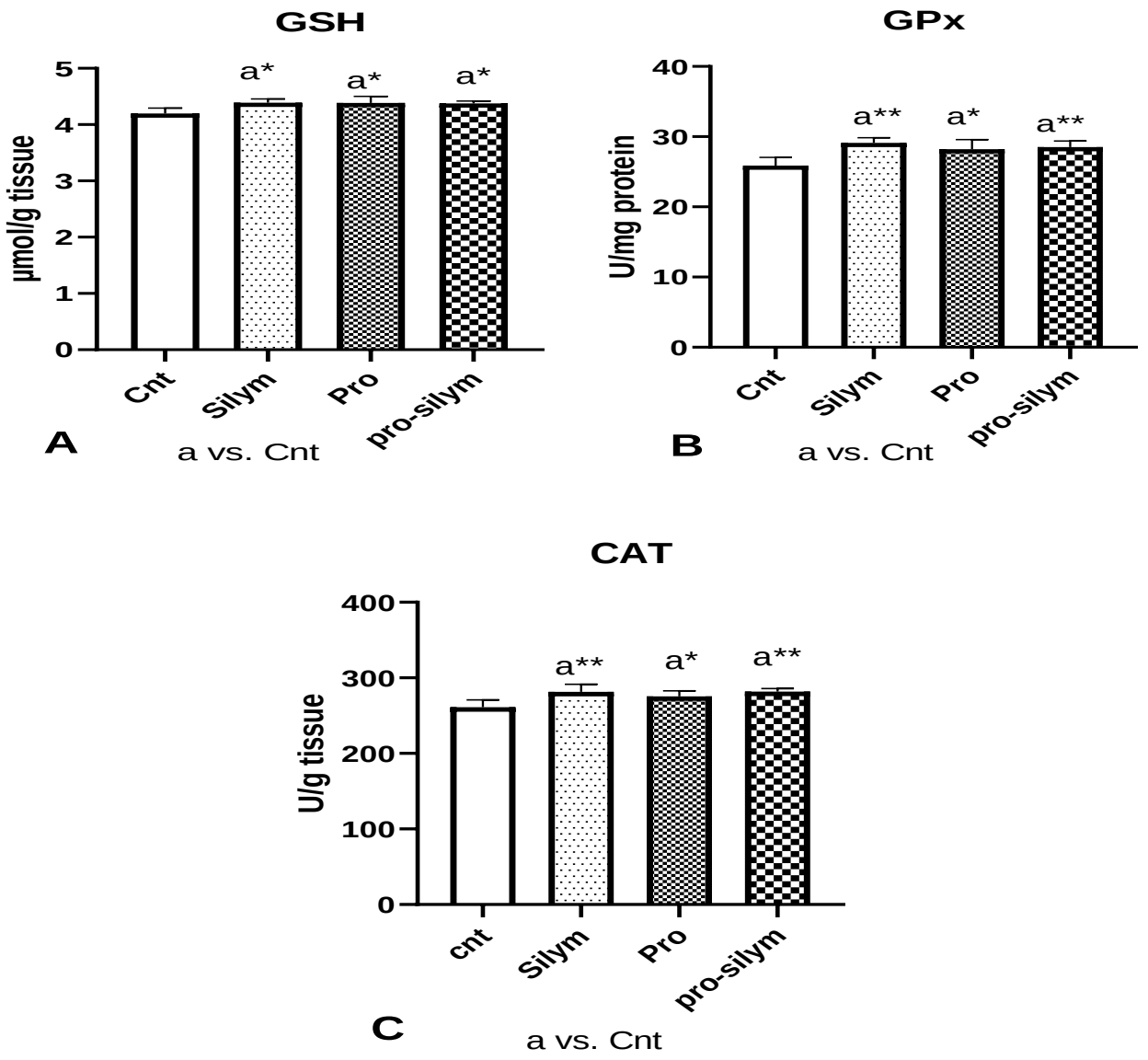

Figure 3: Effects of propofol and silymarin on (A) GSH, (B) GPx, and (C) CAT in liver tissue. Animals were treated with silymarin and propofol, as described in Figure 1. Values are expressed as mean ± SD (n=5). The results show that the treatment of propofol and silymarin together has synergistic favorable effects on the antioxidant parameters of the liver tissue. *P<0.05 and **P<0.01.

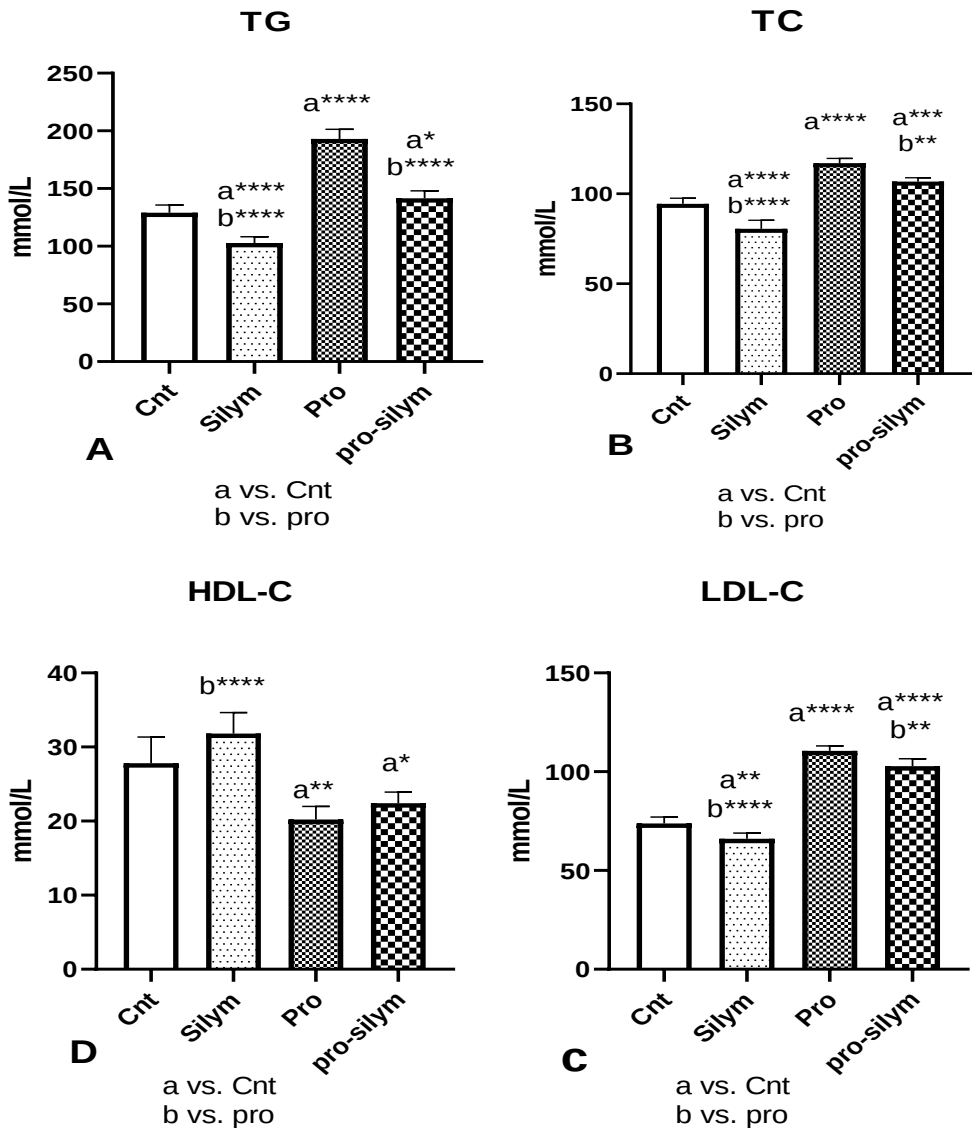

Figure 4: Effects of silymarin and propofol treatment on (A) TG, (B) TC, (C) LDL-C, and (D) HDL-C in plasma. Animals were treated with silymarin and propofol, as described in Figure 1. The results show that the treatment of propofol significantly increased TG, TC, and LDL-C, while it decreased HDL-C in plasma. Favorable effects of silymarin were seen on adverse effects caused by propofol administration (silymarin-propofol group compared to propofol group). ∗P<0.05, ∗∗ P<0.01, ∗∗∗ P<0.001, and ∗∗∗∗ P<0.0001. Values are expressed as mean ± SD (n=5).

Effects of silymarin and propofol on the liver tissue histopathology: In either the silymarin or propofol group, the level of liver cell necrosis showed a significant decline as compared to those of the controls (P<0.01). In the combined propofol-silymarin group, although the number of liver cell necrosis was reduced compared to the controls, the histological alterations were insignificant (P>0.05). Leukocyte infiltration in the propofol group showed a significant rise compared to both the controls and silymarin group (P<0.001).

In the silymarin group, sinusoidal dilations were significantly less than those found in the controls (P<0.05). Although the extent of sinusoidal dilations was reduced in the combined propofol and silymarin group, compared to the controls, it was insignificant (P>0.05). The central vein congestion in both the silymarin and propofol groups showed a significant decline as compared to those of the controls (P<0.001). See Figure 5 and Table 1.

Table 1: Effects of propofol and silymarin on the liver histological parameters.

Parameters	Sham (A)	Silymarin (B)	Propofol (C)	Silymarin+ Propofol (D)
Necrosis	1.71±0.33	0.48±0.02$$	0.63±0.07$$	1.25±0.17*
Leukocyte infiltration	0.52±0.07	0.41±0.04	1.13±0.14$$$***	0.67±0.07
Sinusoidal dilation	0.9±0.17	0.42±0.06$	0.5±0.05	0.84±0.09*
Central venous congestion	1.25±0.16	0.49±0.04$$$	0.51±0.04$$$	1.12±0.12**

Values are given as mean ± SEM. Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. *P<0.05, **P<0.01, ***P<0.001 versus silymarin. $ P<0.05, $$ P<0.01, $$$$P$<0.001 versus controls.

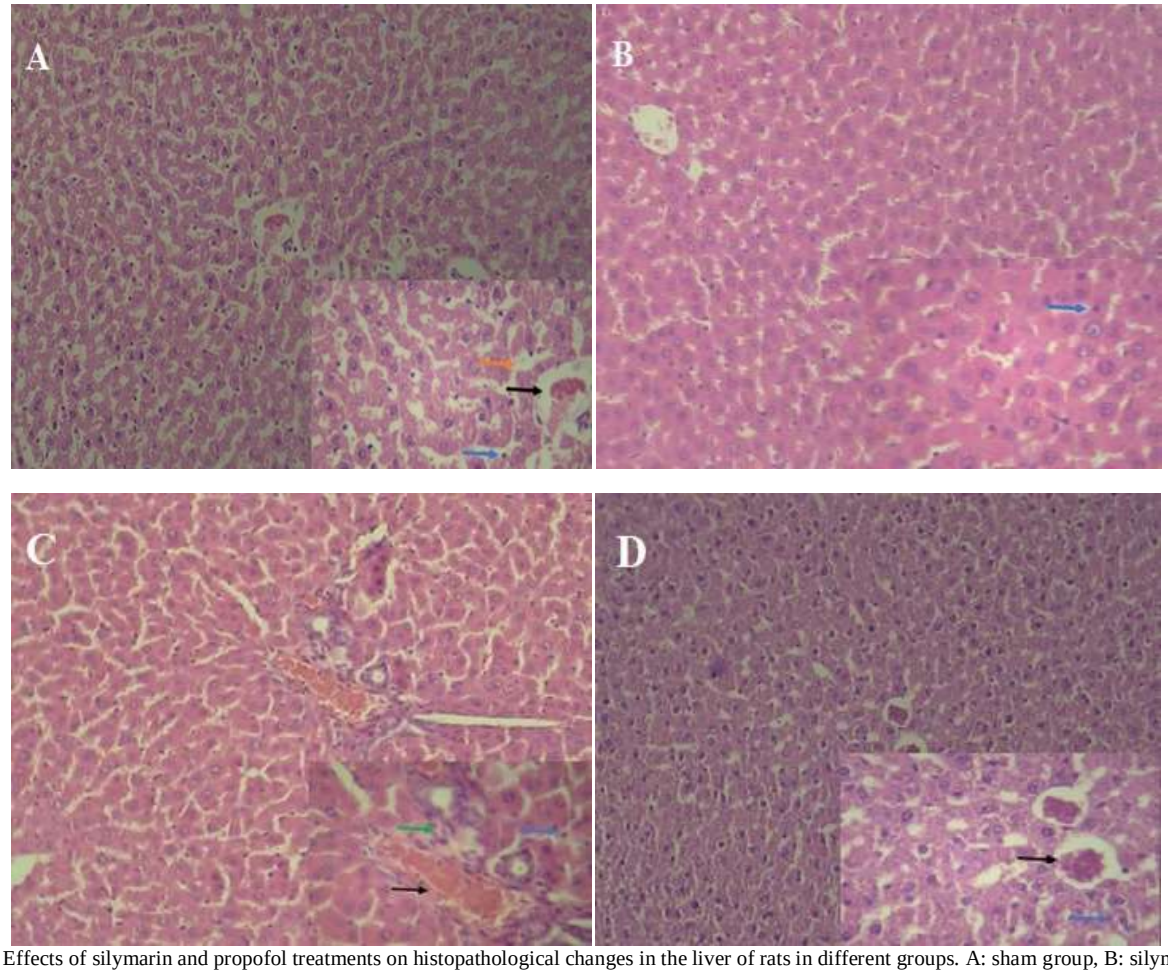

Figure 5: Effects of silymarin and propofol treatments on histopathological changes in the liver of rats in different groups. A: sham group, B: silymarin group, C: propofol group, D: combined silymarin-propofol group. Photomicrographs staining & magnification (H&E stain; 100× and 400×). Black arrows point to the central venous congestion. Green arrows point to leukocyte infiltration. Orange arrows point to the sinusoidal dilation. Blue arrows point to the cell necrosis in liver tissue samples.

Discussion

Studies have shown that silymarin is a good source of natural antioxidant and immunomodulatory compounds [33, 34]. Other studies have demonstrated that silymarin relieves hepatotoxicity thanks to its antioxidant and membrane protection capacities [34]. More recent research has suggested that silymarin protects against tissue necrosis, central vein congestion, and sinusoidal dilation in the liver [33-35].

In recent decades, propofol has been a strong intravenous hypnotic agent and a popular anesthetic drug due to its low side effects and rapid efficacy [8]. The few adverse effects of this drug include metabolic changes and secondary hyperlipidemia [36, 37]. Additionally, propofol has antioxidant properties both *in vitro* and *in vivo* [14]. The antioxidant activity of propofol has been confirmed in laboratories based on various tests. Further, it has been demonstrated that propofol prevents lipid peroxidation and free radical chain reactions [14, 15]. Propofol protects against hepatic ischemia and reperfusion injury in the liver [38]. Chang *et al*. have demonstrated that propofol reduced the invasion and growth of tumor cells in the liver [39].

The purpose of this experimental study was to investigate the various effects of silymarin and propofol primarily on the liver biomarkers. We also examined the effect of silymarin on the hyperlipidemia induced by propofol in male Wistar rats. Thus, we evaluated the silymarin and propofol administration, both separately and concurrently, on liver enzymes, antioxidant factors, and oxidative stress based on histopathological changes and serum lipid factors. Primarily, we documented the beneficial effects of silymarin and propofol on raising the antioxidant enzymes and lowering the MDA levels. These observations were consistent with the results of numerous studies conducted previously [15, 34, 40, 41].

Given the application of propofol as a popular anesthetic drug and its hyperlipidemic side effect, we examined the severity of the hyperlipidemia and the moderating effect of silymarin on propofol. The findings of this study demonstrated that propofol increased such lipid parameters as serum TC, TG, and LDL while lowering the HDL. In this context, propofol is likely to be hazardous to patients with hyperlipidemia. We found that silymarin reduced the adverse effects of propofol and increased the HDL level in rats.

The administration of silymarin and propofol boosted such enzyme activities as AST, ALT, ALP, and LDH, the levels of which were significantly high in some cases. These findings were consistent with those of

former studies while disagreed with some others [42-45].

The examination of MDA, GSH, GPx, and CAT levels in the liver tissue showed a decrease in lipid peroxidation biomarkers and an increase in the activity of tissue antioxidant enzymes. These results were consistent with those reported by earlier studies [45, 46]. The assessment of MDA, GSH, GPx, and CAT demonstrated that the concurrent administration of propofol and silymarin produced favorable synergistic effects. Comparing the effect of propofol and silymarin on GPx and CAT, we found that silymarin had a stronger effect.

In the current study, propofol lowered tissue necrosis, leukocyte infiltration, and central vein congestion in the rat liver. Thus, it can be concluded that propofol has a favorable effect on the liver tissue. Despite the many benefits of propofol, its hyperlipidemia side effect may be harmful to some patients with high levels of serum lipids. Therefore, the findings of this study are beneficial to the management of propofol-induced hyperlipidemia in some patients.

The findings of this study can be promising in the management of patients with hyperlipidemia who are often candidates for anesthesia with propofol administration. The significant increases in the serum lipids caused by propofol may be attributed to the lipid structure of the drug itself. Finally, since no adverse effects were observed in this study for the combined use of silymarin and propofol, the combination can be a promising approach toward the management of the adverse effects of propofol in patients with hyperlipidemia.

Conclusions

This research showed that propofol and silymarin have favorable effects on the liver while improving the antioxidant levels in this organ. Propofol lowered tissue necrosis, leukocyte infiltration, and central vein congestion in the rat liver. Propofol significantly increased the levels of serum lipids. The hyperlipidemia that is induced by the use of propofol can be safely lowered with silymarin. This finding can be promising for the management of patients with hyperlipidemia who may need propofol for anesthesia.

Conflict of Interests

The authors declare no conflict of interests with any internal or external entities.

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Compliance with Ethical Guidelines

The animal care protocol was approved by the Institutional Animal Ethics Committee (Registration #: IR.DUMS.REC.1398.047; Proposal #: 1687; dated 06.01.2020), Dezful University of Medical Sciences, Dezful, Iran.

Authors' Contributions

All authors contributed to the concept and design of the study, as well as the writing and revision of the article. They participated fairly equally in data collection, analyses, interpretation, and writing the various drafts of the manuscript. All authors reviewed and approved the drafts and final version of the manuscript prior to submission to this journal for publication.

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