Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

The Protective Effect of Betaine on Inhibition of Rifampin-Induced Liver Damage in Rats

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Article Type

Research Paper

Received:
Jun 9th 2023
Revised:
Oct 11st 2023
Accepted:
Nov 12nd 2023

ABSTRACT

Background and Objective: Rifampin is one of the antibiotic drugs that is usually used to treat tuberculosis and is considered a strong toxic agent for the liver. Therefore, this study was conducted to investigate the effects of betaine administration on rifampin-induced liver damage in rats.

Methods: This experimental study was conducted on 60 male Wistar rats in 6 groups of 10. Liver damage and induction of oxidative stress were caused by oral administration of rifampin 100 mg/kg of body weight for 14 consecutive days. Different doses of betaine (10, 50 and 100 mg/kg of body weight) were administered by gavage to the sick rats. At the end of the treatment course, liver damage caused by rifampin was investigated by examining serum biochemical factors (ALT, AST, LDH, Bilirubin), and reactive oxygen species (ROS), glutathione (GSH), antioxidant capacity (FRAP), and lipid peroxidation (LPO), and histopathological changes in liver tissue were evaluated.

Findings: Serum ALT level in the group that received rifampin (201±7821) was significantly higher than the control group (26±281) (p=0.0031). The serum level of AST in the group that only received rifampin (684±118) was significantly higher than the control group (50±1021) (AST=706). The amount of ROS was also significantly increased in the patient group (216,000±1001) compared to the control group (982,090±8332) (p=0.002). Also, the amount of LPO in the group that received rifampin (8.24±1.63) increased significantly compared to the control group (1.19±0.13) (p=0.021).

Conclusion: The results of the study showed that betaine can reduce liver damage caused by rifampin and its consequences.

Keywords: *Betaine, Liver Damage, Rifampin, Oxidative Stress.*

Cite this article: Peiravi P, Mohammadi H, Rashidiani-Rashidabadi A, Mohammadi M, Adineh A. The Protective Effect of Betaine on Inhibition of Rifampin-Induced Liver Damage in Rats. *Journal of Babol University of Medical Sciences*. 2024; 26: e58.

[DOI: 10.22088/jbums.26.1.58]

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Introduction

Liver has an important role in regulating physiological processes. Liver is involved in various vital functions including metabolism, secretion and storage. In addition, detoxification of various drugs and xenobiotics occurs in the liver. Therefore, liver diseases are considered serious health problems. Liver diseases may be classified into acute and chronic hepatitis, hepatosis and cirrhosis. Liver diseases are caused by toxic chemicals, alcohol consumption, infections and autoimmune disorders (1). Today, the only way to cure cirrhosis is liver transplantation. Due to the lack of donors and the existence of diseases that can be transmitted to people as a result of this transplant, as well as the recurrence of the disease and the destruction of the liver, the percentage of treatment has decreased, and scientists have turned to anti-fibrosis treatments in order to find new treatment methods (2).

Tuberculosis continues to be a public health issue all over the world, especially with the spread of AIDS, it is one of the major causes of death in adult patients (3). Rifampin, which is an antibiotic commonly used to treat tuberculosis, is considered a strong toxic agent for the liver (4). Clinical hepatitis has been reported in 1.1% of elderly people treated with rifampin (5). The mechanism of liver damage caused by rifampin has not been fully clarified yet. Some studies have shown that rifampin leads to lipid peroxidation and depletion of the antioxidant tripeptide glutathione (GSH) and free radical scavenging enzymes through oxidative damage (6).

In a study conducted by Yang et al., it was found that the consumption of rifampin significantly increased the levels of malondialdehyde and decreased the activity of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase enzymes (7). Furthermore, in a study by John et al., it was found that the free radicals resulting from the reaction of rifampin metabolites with oxygen cause the peroxidation of membrane lipids, which itself leads to the formation of lipid peroxides (malondialdehyde) and ultimately the loss of hepatocyte membrane integrity and liver damage (8).

A study by Ghasemian Yadegari et al. also suggested the liver damage of rifampin as a result of increased oxidative stress markers and decreased antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase) in rats treated with this drug (9). Several studies have shown that liver cell damage in rifampin poisoning occurs due to the production of oxygen free radicals and the reduction of the body's antioxidant system, which is a sign of oxidative stress (10, 11). Therefore, conditions of oxidative stress and subsequent liver damage caused by rifampin are among the mechanisms of pathogenesis involved in hepatotoxicity caused by rifampin. Since oxidative stress plays a major role in the occurrence of pathophysiological changes in the liver in rifampin hepatotoxicity, therefore, the use of strong antioxidants as protective compounds can be very helpful in this regard.

As a quaternary ammonium compound, betaine is also known as trimethylglycine, glycine betaine and oxyneurine (12). Betaine is present in microorganisms, plants and animals (13). This compound is a derivative of glycine amino acid and has three biochemically active groups in the form of methylamine (14). Another important effect of betaine that most researchers have emphasized on is the antioxidant activity of betaine. In several studies, the beneficial antioxidant properties of betaine in trapping free radicals and reducing oxidative stress have been abundantly mentioned in the tissues of the brain (15), kidney (16), testis (17) and the liver (13, 18, 19) of rats. In normal conditions of the body, reactive oxygen species produced by the antioxidant defense system are neutralized. However, in conditions such as excessive production of these active mediators or insufficient antioxidant system, it causes oxidative stress in the cell and damages proteins, lipids, proteins, and DNA (20-22). Since betaine is a strong and potential antioxidant, it leads to

[DOI: 10.22088/jbums.26.1.58]

the reduction of oxidative stress by trapping free radicals, and the beneficial effects of betaine in liver tissue have been observed in previous studies. Therefore, the aim of this study is to investigate the protective effects of betaine administration on inhibition of rifampin-induced liver damage in rats.

Methods

After approval by the ethics committee of Lorestan University of Medical Sciences with the code IR.LUMS.REC.1401.037, this experimental study was carried out in 2022 at the Faculty of Pharmacy of Lorestan University of Medical Sciences. All ethical principles were carried out according to the international guidelines for working with laboratory animals. Antioxidant betaine (trimethylglycine) was purchased from Sigma-Aldrich, and rifampin was purchased from Khorramabad pharmacies. To conduct this study, 60 male Wistar rats with an approximate weight of 220±20 grams were randomly divided into 6 groups of 10 as follows:

1) The control group only received normal saline.
2) The control group received only 100 mg/kg/day of rifampin for 14 consecutive days (9).
3) The treatment group that received 100 mg/kg/day rifampin for 14 consecutive days + 10 mg/kg/day betaine for 14 consecutive days (18).
4) The treatment group that received 100 mg/kg/day rifampin for 14 consecutive days + 50 mg/kg/day betaine for 14 consecutive days.
5) The treatment group that received 100 mg/kg/day rifampin for 14 consecutive days + 100 mg/kg/day betaine for 14 consecutive days.
6) Betaine group that received 100 mg/kg/day (the highest dose) of betaine for 14 consecutive days.

Feeding and maintenance conditions were considered the same for all groups (in the form of 12:12 light-dark cycle and a temperature of 21±2°C). The same food and water were freely available to the animals. For gavage, based on the weight of the animal, rifampin and betaine were prepared in separate vials with a suitable needle and administered in equal volumes of 1 ml. It should be noted that rifampin was given through gavage feeding one hour before betaine administration. At the end of the test period and 24 hours after the last injection, to measure biochemical factors including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and total bilirubin, fasting blood samples were collected from the chest area and left side of the animal's body. The serum of the blood samples was separated by centrifugation (2500 rpm, for 15 minutes at 30°C) (23, 24).

To determine the antioxidant status of the liver, all rats were sacrificed after anesthesia by cervical dislocation. The livers of rats were immediately removed and washed in very cold normal saline. Then 10% homogenate was prepared in 1.15% (W/V) potassium chloride. The homogenate was centrifuged at 7000 rpm for 10 minutes at 4 °C. Based on standard protocols, the supernatant solution was used to measure lipid peroxidation (LPO), reactive oxygen species (ROS), total antioxidant capacity (FRAP) and glutathione (GSH) levels based on previous protocols (25-28). For histopathological investigations, liver samples were fixed in formalin buffer solution (0.4% monobasic sodium phosphate, 0.64% dibasic sodium phosphate, and 10% formaldehyde in distilled water). The tissue section was prepared using paraffin with a diameter of 5 microns and was prepared using hematoxylin and eosin (H&E) staining for observation under a light microscope (29).

Statistical analysis was performed by Graphpad Prism 6 (at least three repetitions in each experiment), and the results were reported as Mean±SEM and the comparison between different groups was done using one-way analysis of variance (ANOVA) and then statistical analysis was done using Tukey's multiple comparison test, and $p<0.05$ was considered significant.

[DOI: 10.22088/jbums.26.1.58]

Results

The results of biochemical biomarkers in this study showed that in the rats of the toxic drug group (rifampin), the serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) enzymes increased significantly compared to the control group ($p<0.05$). In the betaine treatment group, the increased serum levels of ALT, AST and LDH enzymes caused by rifampin decreased significantly ($p<0.05$) (Figure 1).

The results of the investigation of oxidative stress indicators in this study showed that the level of lipid peroxidation and reactive oxygen species (ROS) in animals receiving rifampin was higher than the control group. The use of betaine reduced lipid peroxidation and reactive oxygen species (ROS) in different study groups (Figure 2, Table 1). The level of reduced glutathione and the amount of antioxidant capacity in the liver tissue were also measured (Figure 2, Table 1). It was observed that the level of glutathione and the antioxidant capacity of the liver reached its lowest level in the group exposed to rifampin (Figure 2, Table 1). The use of betaine prevented glutathione depletion in different studied groups (Table 1).

Histopathological changes in the liver tissue of the tested animals showed that when rifampin is administered to the animals, liver tissue changes occur in the form of necrosis, sinusoidal congestion and inflammation of ducts in the liver tissue. In groups receiving betaine at different doses, tissue damage caused by rifampin administration was reduced (Figure 3).

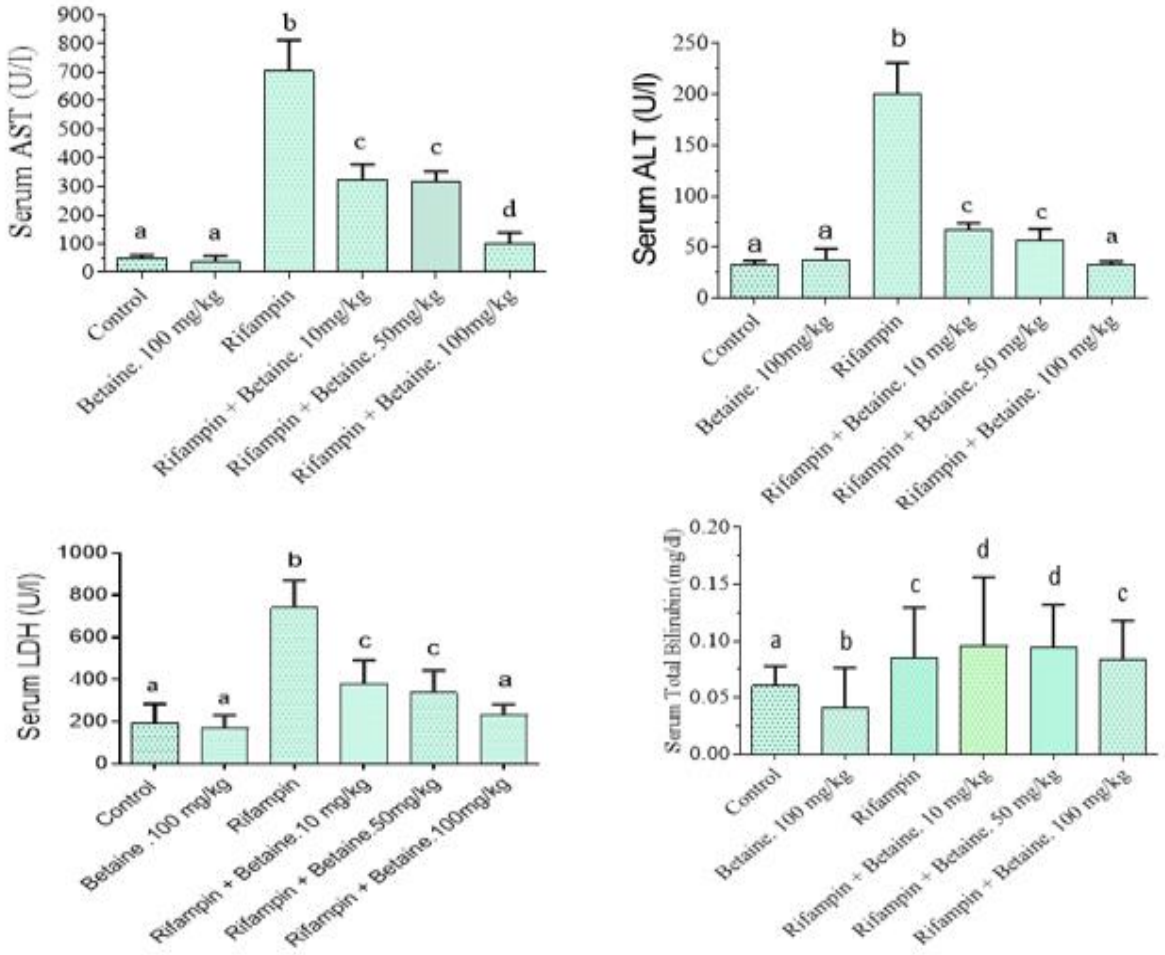


Figure 1. The results of evaluating biochemical biomarkers

[DOI: 10.22088/jbums.26.1.58]

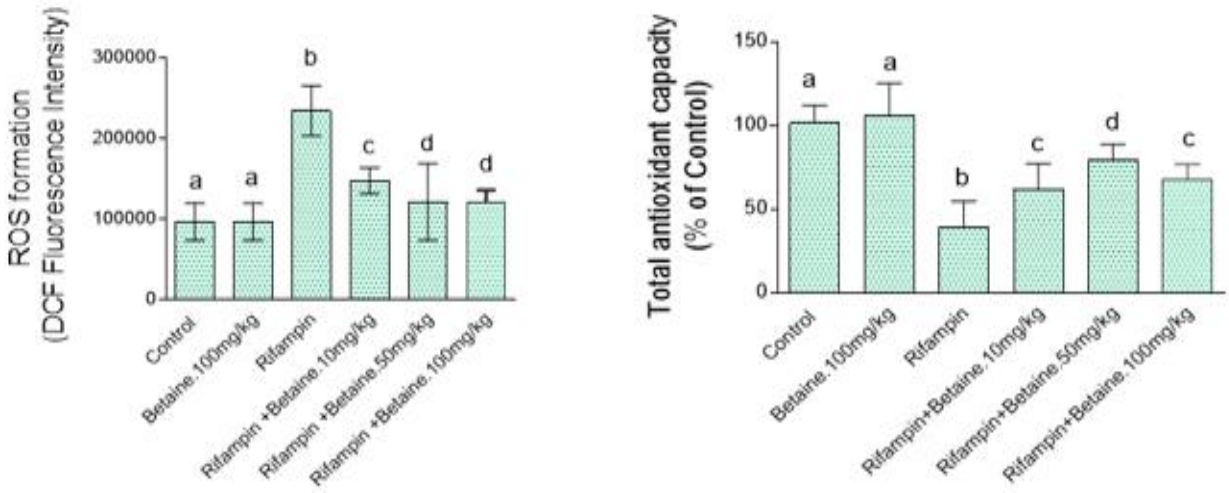


Figure 2. The results of examining oxidative stress indicators

Table 1. Investigation of the level of lipid peroxidation and glutathione level of liver tissue in different study groups and investigation of the effect of betaine administration on it

Study groups	Lipid peroxidation (nmol/mg wet tissue)	Glutathione levels (µmol/mg wet tissue)
Control	2.08±0.06[a]	70.95±3.10[a]
Betaine (100 mg/kg)	2.32±0.29[a]	69.19±6.21[a]
Rifampin	9.63±0.82[b]	18.24±5.57[b]
Rifampin + Betaine (10 mg/kg)	4.19±0.34[c]	29.27±8.69[c]
Rifampin + Betaine (50 mg/kg)	4.34±0.54[c]	32.62±6.01[c]
Rifampin + Betaine (100 mg/kg)	2.96±0.09[c]	43.19±6.51[c]

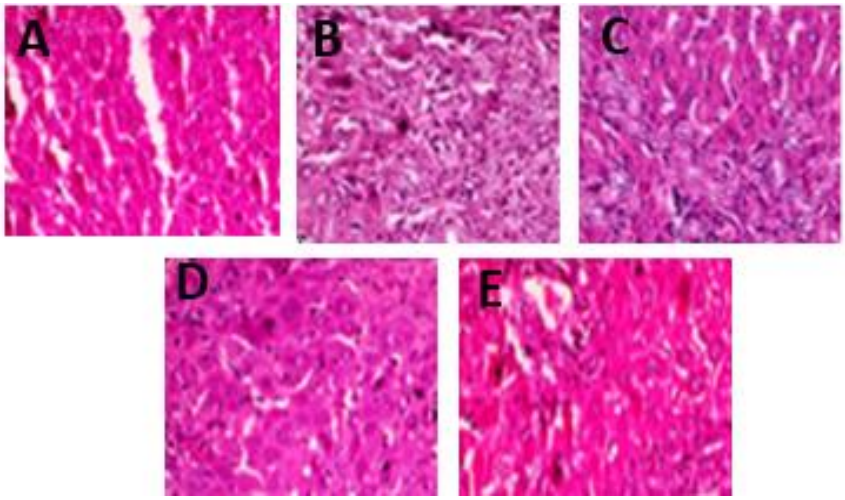


Figure 3. Liver histopathological changes in animals treated with betaine. A: control, B: rifampin (100 mg/kg/day), C: group receiving rifampin+betaine (10 mg/kg/day), D: group receiving rifampin+betaine (50 mg/kg/day), E: group receiving rifampin+betaine (100 mg/kg/day)

[DOI: 10.22088/jbums.26.1.58]

Discussion

In the present study, the administration of rifampin in rats caused a significant increase in the serum levels of ALT, AST and LDH enzymes compared to the healthy control group, which is consistent with the findings of other researchers (9, 30). In general, an increase in the serum level of the above enzymes indicates the occurrence of necrosis and damage to the membrane structure of hepatocytes (31).

In this study, betaine administration led to a significant decrease in the serum levels of ALT, AST, and LDH enzymes compared to the healthy control group, which is consistent with the results of Heidari et al., Esfahani et al., Hasanzadeh-Moghadam et al., and Wang et al. (18, 32-34). The return of increased levels of serum enzymes indicative of rifampin-induced liver damage to their normal state by betaine can be due to the prevention of the leakage of intracellular enzymes by maintaining the integrity of the cell membrane or the regeneration and repair of damaged liver cells (35).

In the present study, the use of rifampin significantly increased the level of lipid peroxidation. The results of the present study were consistent with the findings of Ghasemian Yadegari et al. and Santhosh et al. (9, 36). Rifampin is a strong inducer of the cytochrome P450 system, which causes the production of toxic metabolites from drugs and their covalent binding to liver macromolecules (37). Therefore, the conversion of rifampin into active metabolites that are able to bind to macromolecules in hepatocytes leads to liver damage (38). The findings of the present study confirmed the above mechanism; because a significant increase in the amount of lipid peroxidation was observed in the liver tissue of rats receiving rifampin, which was observed along with a significant decrease in antioxidant enzymes.

The free radicals resulting from the reaction of rifampin metabolites with oxygen cause the peroxidation of membrane lipids, which itself leads to the formation of lipid peroxides and finally the loss of hepatocyte membrane integrity and liver damage (39).

The level of lipid peroxidation in liver cells was significantly reduced by administering betaine along with rifampin. Betaine is a strong antioxidant that reduces lipid peroxidation in liver cells by reducing free radicals (40).

The present study demonstrated that different doses of betaine (10, 50 and 100 mg/kg) effectively prevent oxidative stress and subsequent mechanisms in the liver tissue of rats. Hence, a large part of the protective effects of betaine in treated mice could be exerted through the reduction of free radicals as a result of betaine consumption. Because it has been found that free radicals increase DNA damage (41) and changes in the cellular skeleton (42). The excessive increase of free radicals in the liver due to rifampin leads to a decrease in the capacity of antioxidant enzymes. In this research, it was found that the capacity of antioxidant enzymes decreased significantly in rats that received rifampin. On the other hand, after the administration of betaine in the studied groups, the amount of antioxidant enzymes increased significantly, so betaine can increase the power of the antioxidant system by inhibiting free radicals and improving the liver cells and compensate for the antioxidant activity. In this sense, the results of the present study are consistent with the results of Alirezaei et al., Zhai et al., and Abdelrazek et al. (43-45).

Superoxide dismutase, catalase and glutathione peroxidase are antioxidant enzymes that have formed a defense system against reactive oxygen species (ROS) (46). In the present study, a significant decrease in hepatic glutathione levels was achieved after the use of rifampin. Taking betaine along with rifampin led to a significant increase in the level of glutathione; therefore, the higher the amount of betaine was consumed, the level of glutathione in liver cells increased significantly, which could be due to the improvement of liver cells after betaine administration. In the results of studies by Alipourfard et al. and Alirezaei et al., this increase in glutathione level was observed as a result of betaine consumption (47, 48).

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The beneficial role of betaine in liver tissue has been well demonstrated. Several mechanisms have been proposed for the cytoprotective properties of betaine. One of the most important of these mechanisms is the antioxidant activity of betaine, which has been mentioned in previous studies (47, 48). Oxidative stress and mitochondrial dysfunction are two related cellular events.

In this study, extensive degenerative changes and necrosis of the center of the lobules were caused by rifampin. The histopathological findings about the liver in this study reflect the direct and obvious toxic effects of rifampin. With the administration of betaine, along with rifampin, only mild degenerative changes were observed and no trace of necrosis was seen, which showed the protective effects of betaine against the hepatotoxicity of rifampin. Overall, the obtained results confirm the protective role of betaine on rifampin hepatotoxicity. Therefore, after conducting randomized clinical trials, betaine can be used in humans who take rifampin to prevent irreparable liver damage. However, the exact knowledge of the substance, the precise determination of the location and the effective mechanism or mechanisms in its pharmacological action in this case require future studies.

Acknowledgment

We hereby thank the Vice-Chancellor of Research and Technology of Lorestan University of Medical Sciences for approving and financially supporting this research as well as all the participants.

[DOI: 10.22088/jbums.26.1.58]

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[DOI: 10.22088/jbums.26.1.58]