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Original Article

L-carnitine Protects Cisplatin Induced Liver Fibrosis in Experimental Animals via Reducing Oxidative and Nitrosative Stress

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ABSTRACT

Background: The aim of the present study was to examine the protective potential of L-carnitine against Cisplatin-induced liver fibrosis in experimental models. **Materials and Methods:** The rats were randomly divided into five groups, each containing an equal number of animals (*n* = 6). Repeated doses of Cisplatin were used to promote liver fibrosis, and serum parameters like aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin (TB), and albumin were assessed, as well as hepatic hydroxyproline (HP), reduced glutathione (GSH), and malondialdehyde (MDA), Superoxide dismutase (SOD), and pro-inflammatory cytokines. A Western blot was used to quantify iNOS expression, and liver tissue was also processed for histological examination (H&E staining). **Results:** In this investigation, we discovered that Cisplatin decreased body and liver weight in rats, whereas L-carnitine administration resulted in normal body and liver weight. Cisplatin rats had higher levels of serum parameters (AST, ALT, total bilirubin) as well as oxidative parameters like GSH, MDA, and inflammatory-cytokines. Treatment with L-carnitine reduced oxidative stress and suppressed the release of cytokines in a dose-dependent manner, as well as providing protection against fibrosis. In cisplatin-treated rats, iNOS expression was found to be 1.8 times higher. Furthermore, increased iNOS expression was dose-dependently reduced after treatment with L-carnitine. **Conclusion:** According to the findings, L-carnitine has a protective effect against Cisplatin-induced liver fibrosis.

Keywords: Cisplatin, Liver Fibrosis, GSH, L-carnitine, Cytokine.

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INTRODUCTION

Extracellular matrix (ECM), a hallmark of liver fibrosis accumulates excessively in the liver in chronic liver diseases such as viral hepatitis and alcoholic or non-alcoholic steatohepatitis.[1] Various cellular and molecular mechanisms are involved hepatic fibrosis. Not all disorders of liver results in liver fibrosis, but those involved can have a significant impact in liver function. An imbalance in ECM production and its degradation leads to liver fibrosis in the medium to long term effects. Balance between MMPs and TIMPs (Tissue inhibitors of matrix metalloproteinases) is essential for regulation of ECM homeostasis.[2–3] Several biochemical parameters, such as aspartate AST, ALT, HP and TB, have been reported as biochemical markers for liver pathogenesis in various studies.[4] These indicators are critical to understanding progression of liver fibrosis. Release of cytokines are increased with the advancement of liver insult and they are known to be an essential factor contributing in the progression of liver fibrosis. Many higher plants and microorganisms contain the quaternary amine carnitine (hydroxy-trimethylaminobutyrate).[5-6] It was first discovered in 1905, it was given the Latin name "carnis" for "muscle" (flesh or meat). Consequently, several larvae in the same family as the mealworm (Tenebriomolitor) have been given the moniker "Vitamin B," which refers to L-carnitine. These insects require a small amount of vitamin B to maintain their normal growth and development. L-carnitine is conditionally synthesized by humans and other higher animals in limited amount. L-carnitine is also termed as an analogue to vitamins.[7–8] Several pharmacological actions of L-carnitine have been reported, which includes anti-inflammatory, anti-oxidant, anti-arthritic, anti-Alzheimer, hepatoprotective, and anti-cancer activity.[9-11] The aim of this study the protective effect of L-carnitine in liver fibrosis.

MATERIALS AND METHODS

Animals

Wistar rats weighing between 180 and 250gm were used in this investigation. Animals were as per standard condition with free access to food and water, maintained at a controlled temperature of about 22–240 C and 65% humidity, with a normal light–dark cycle (12-hr light–dark cycle). The experimental protocol was approved by the IAEC (Approval No. IAEC/MCP/001/2020).

Drugs and chemicals

Cisplatin was purchased Venus Remedies Ltd, India and ELISA kits for IL-6, TNF-, and IL-1, (procured from eBioscience, United States,) and AST, ALT, TB, HP and ALP kits (Erba Diagnostics in India). All of the other reagents used were laboratory grade.

Induction of liver fibrosis

Liver fibrosis was induced by injecting Cisplatin at a dose of 3 mg/kg at repeated doses on the 0, 7th, 14th, and 21st days of the 4-week study (Cisplatin diluted up to 1 ml by using distilled water).[12]

Experimental design

All animals were equally divided into seven group (*n*=6)

Group 1: Normal Control - Rats received 1 ml/day of 0.5% CMC (carboxymethyl cellulose) solution

Group 2: Disease Control - Received Cisplatin (3 mg/kg.) at 0, 7th, 14th and 21st days by intraperitoneal (i.p.) route

Group 3: T1 (C100)- Received Cisplatin (3mg/kg.) at 0, 7th, 14th and 21st days by intraperitoneal (i.p.) route + L-carnitine (100 mg/kg/day) by oral route

Group 4: T2(C300)- Received Cisplatin (3mg/kg.) at 0, 7th, 14th and 21st days by intraperitoneal (i.p.) route + L-carnitine (300 mg/kg/day) by oral route

Group 5: T3(C500)- Received Cisplatin (3mg/kg.) at 0, 7th, 14th and 21st days by intraperitoneal (i.p.) route + L-carnitine (500 mg/kg/day) by oral route

Preparation of L-carnitine dose

L-carnitine was suspended in 0.5 % CMC solution freshly for each daily treatment. In brief, every day 2 gm of L-carnitine was suspended in a 20 ml solution of 0.5 % CMC means each ml consists of 100 mg/ml L-carnitine.

Collection of blood samples

The rats were anaesthetized with a light ether anesthetic. The blood was collected via the retro-orbital route in eppendorf tubes and serum was separated using a cooling centrifuge at 10000 rpm for 10 min. The serum samples were kept at -20°C until they were analysed.[13]

Body weight and Liver weight

The body weight of each group rat was measured on Day 0 and Day 28 respectively. At the end of the study, after euthanasia of the animal the liver weight of each rat was measured. The liver was removed and washed in ice-cold phosphate buffered saline solution before being blotted on filter paper and weighed. One part of the liver tissue was used for histopathology, while the other was used to make the tissue homogenate.[14]

Biochemical Parameters

Assessment of Biochemical paradigms such as AST, ALP, ALT, TB and HP was conducted as per the manufacturer's protocol and the literature avalable.[15]

Assessment of Antioxidant Parameters

Estimation of malondialdehyde of lipid peroxidation in liver tissue

The most significant biomarker of tissue lipid peroxidation is malondialdehyde. Lipid peroxidation occurs when MDA and thiobarbituric acid combine, which results in the formation of a pink colour as a final product was measured at 532 nm absorbance using UV spectrophotometer.[16]

Estimation of Reduced Glutathione

Glutathione concentration in liver tissues homogenate was determined as previously described method by jain *et al*., 2018.[17]

Estimation of Superoxide Dismutase Activity

Superoxide Dismutase concentration in liver tissues homogenate was determined as previously described method by Jain *et al*., 2018.[18]

Determination of iNOS Level

Western blot analysis was used to measure the expression of iNOS. The rat tissue samples were diced and homogenized, then lysed with modified radioimmuno precipitation assay (RIPA) lysis buffer and cellular lysates were then processed for western blotting. A predetermined amount of protein (60 µg) was added and separated using a 10% SDS-polyacrylamide gel electrophoresis (PAGE). A nitrocellulose membrane was used to transfer the proteins. The membrane was then probed with specific antibodies as per manufacturer protocol, and band intensity was measured using densitometry.[19]

Estimation of Pro-inflammatory Cytokines

Assessment of Pro-inflammatory cytokines such as IL-6, IL-1, IL-10, and TNF- in liver tissue homogenate was performed as per the manufacturer's protocol using ELISA kits. The standard curve was used to determine the final concentration.[20]

Histopathology

The liver was isolated kept in 10% formalin solution and embedded in paraffin blocks which was subjected to thin slices and stained with hematoxylin and eosin dye and examined under a microscope for pathological changes and images were captured motic camera system.[21]

USG assisted Elastography

Ultra-sonography (USG) assisted Elstography study of isolated liver for determination of fibrosis was performed before subjecting liver sample for histopath study.

RESULTS

Effect on body weight and liver weight

When compared to the control group, the disease control group's weight increased over the treatment period. Both the L-carnitine (500 mg/kg) and control groups gained weight. When compared to a control group, L-carnitine at a dose of 100 mg/kg had no effect on body weight. We noticed that the control group had a bigger liver weight than the normal group at the conclusion of the study. When compared to the control group, L-carnitine at 500 mg/kg showed the greatest significant effect on liver weight given in Table 1.

Effect on Biochemical Parameters

The control group's levels of AST, ALP, ALT, TB, and HP were considerably greater than those of normal rats. L-carnitine did not affect biochemical marker levels in rats given a 100 mg/kg dosage, whereas rats given 300 and 500 mg/kg doses had lower levels than the control group, as seen in Figures 1 and 2. The increased biochemical levels in the animals in the control group showed that the livers of the rats had been poisoned. Biochemical indicators had no impact in the group given solely L-carnitine at a dose of 500mg/kg.

Table 1: Effect of L-Carnitine on body weight and liver weight.

Group	Body weight (gm)		Liver weight (gm)
	0 Day	28 day	
Normal	183.5± 7.51	196.4±8.36	4.63 ± 0.6
Control	184.9± 4.19	163.9±11.17	7.39 ± 0.7###
C100	184.9±6.21	220.4±11.57	6.51 ± 1.2
C300	181.6±7.28	218.5±9.43	5.73 ± 1.0**
C500	187.5±8.41	216.4±10.27	5.22 ± 0.8***

Data were expressed as mean ± SEM, analysed using one way analysis of variance, *p<0.05, **p<0.01, ***p<0.001 compared to control rats and ##p<0.01, ###p<0.001 is compared with the sham animals.

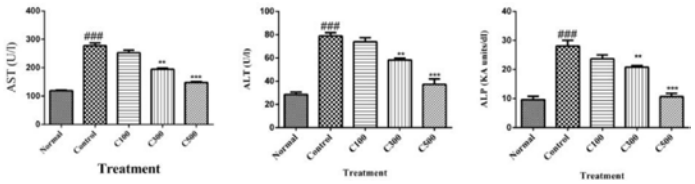

Figure 1: Effect of L-Carnitine on biochemical parameters.
Data were expressed as means ± SEM, $n = 06$. Statistical significance was determined by one-way ANOVA followed by the Dunnet test: Compared with Normal $^{###}p < 0.01$, Compared with Control

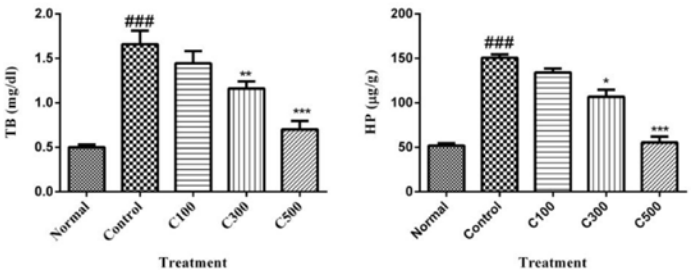

Figure 2: Effect of L-Carnitine on biochemical parameters.
Data were expressed as means ± SEM, $n = 06$. Statistical significance was determined by one-way ANOVA followed by the Dunnet test: Compared with Normal $^{###}p < 0.01$, Compared with Control

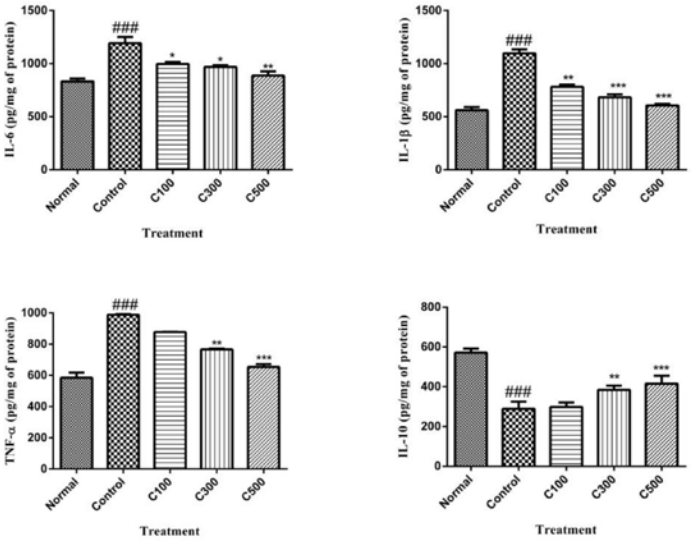

Figure 3: Effect of L-Carnitine on cytokine level.
Data were expressed as means ± SEM, $n = 06$. Statistical significance was determined by one-way ANOVA followed by the Dunnet test: Compared with Normal $^{###}p < 0.01$, Compared with normal; $^{*}p<0.05$; $^{***}p<0.001$ compared to Control

Effect on Serum Cytokine

Pro-inflammatory cytokines such as IL-6, IL-1, and TNF- were found to be higher in the disease control group than in the normal group. When compared to the disease control group, the level of cytokines is significantly reduced after 28 days of L-carnitine (500 mg/kg) treatment. This indicates that L-carnitine inhibits cytokine release. The rats in the L-carnitine-treated group vary significantly from the rats in the control group, as shown in Figure 3.

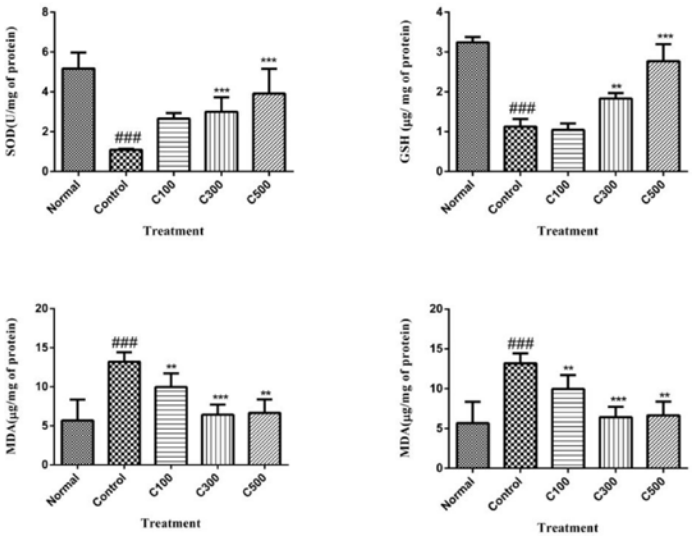

Figure 4: Effect of L-Carnitine on oxidative stress.
Data were expressed as means ± SEM, $n = 06$. A: Lipid Peroxidation; B: GSH; C: Catalase; D: SOD. Statistical significance was determined by one-way ANOVA followed by the Dunnet test: Compared with Normal $^{###}p < 0.01$, Compared with Control

Effect on Oxidative Stress

The levels of SOD and GSH in Cisplatin-induced liver fibrosis rats and the control group were significantly different. However, compared to Cisplatin treatment, 28 days of L-carnitine (at dosages ranging from 100 mg/kg to 500 mg/kg) resulted in dose-dependently greater levels of SOD and GSH. Fibrosis produced by Cisplatin reduced GSH levels as compared to the control group. MDA levels were significantly lower in rats given L-carnitine for 28 days (100, 300, and 500 mg/kg) compared to the disease control group. When compared to the control group, L-carnitine at a dose of 500 mg/kg lowered MDA levels. Catalase activity was lower in the Cisplatin-induced liver fibrosis group than in the control group. Figure 4 shows how oral L-carnitine treatment (300 and 500 mg/kg) for 28 days increased catalase activity significantly when compared to the Cisplatin-treated group.

Effect on iNOS Level

When we treated the rats as described above, we discovered that the expression of iNOS was increased in the Cisplatin-induced liver fibrosis condition. In Cisplatin-treated rats, iNOS expression was found to be 1.8 times higher. Furthermore, increased iNOS expressions were decreased in a dose-dependent manner after treatment with L-carnitine, as shown in Figure 5. Expression of iNOS after inducing rats with Cisplatin and different treatment concentrations of L-carnitine. GAPDH served as loading control.

USG Assisted Elastography

When the animals were euthanized, their liver parenchyma was removed for *ex-vivo* ultrasonography. A jar of physiological serum was used to keep the explants at room temperature before the experiment. We kept the liver explant at room temperature in a plastic container with physiological serum so that we could perform immersion ultrasonography study. To put it another way, control group shear wave velocity is significantly higher than that of the normal group. A decrease in shear wave velocity was found in the L-carnitine-treated animals, as well as normal structure and architecture. Figure 6 depicts the results of the MRI scans.

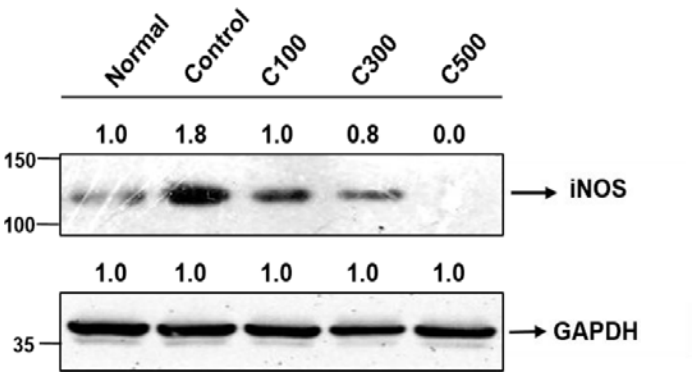

Figure 5: Effect of L-carnitine in Cisplatin induced iNOS expression.

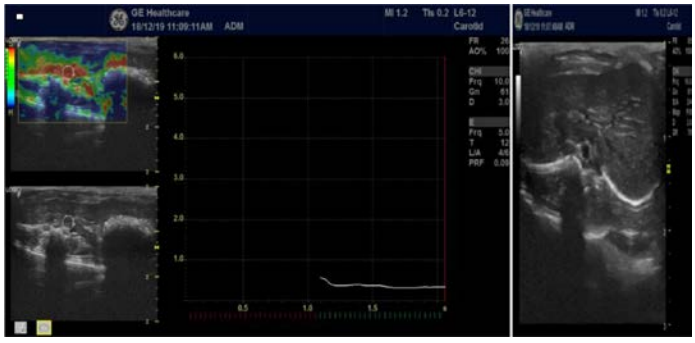

Figure 6A: Elastography and Ultra Sonography of normal.
Liver size: 1.6cm. Elastography score (pKa 0.8).

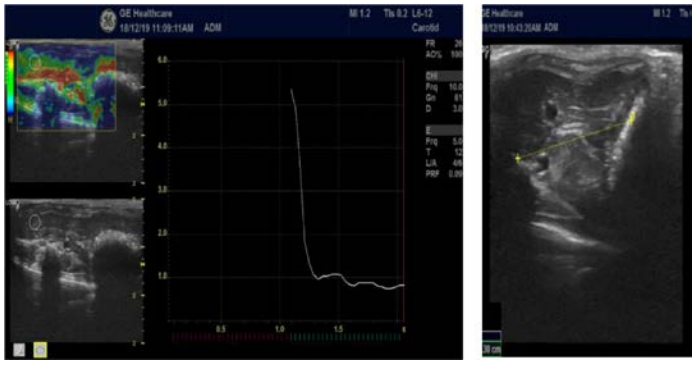

Figure 6B: Elastography and Ultra sonography of diseased control.
Liver size: 2.3cm. Elastography score (pKa-5.2)

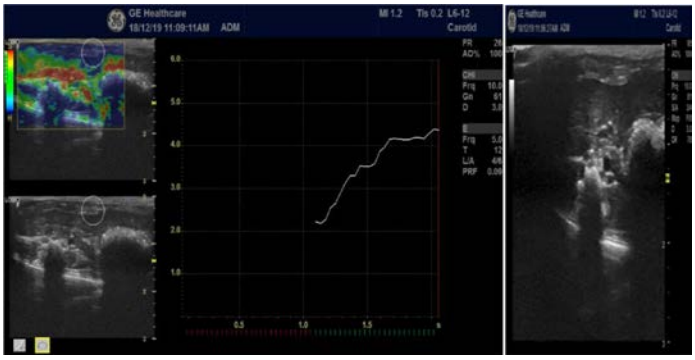

Figure 6C: Elastography and Ultra sonography of C100.
Liver size: 2.0 cm. Elastographic score (pKa-4.2)

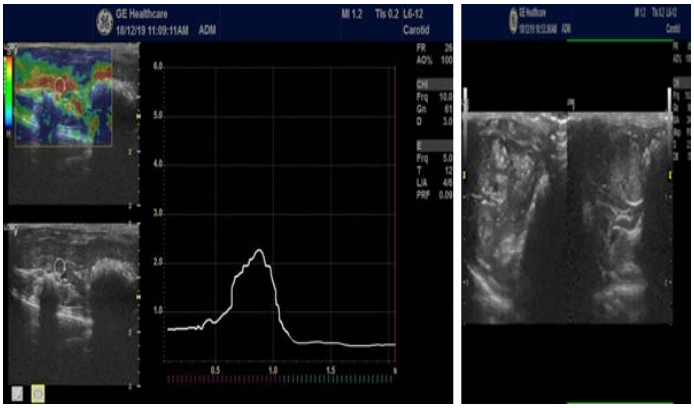

Figure 6D: Elastography and Ultra sonography of C300.
Liver size: 1.6cm. Elastographic score (pKa-1.9)

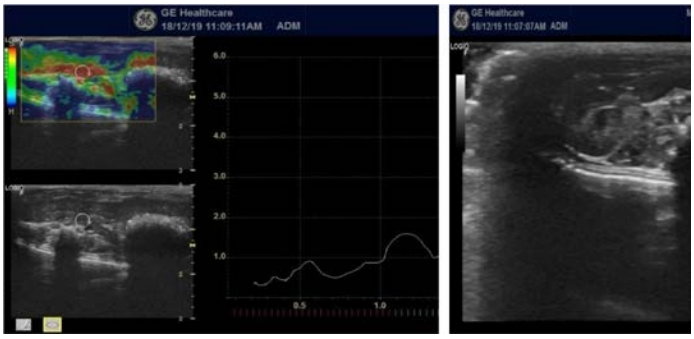

Figure 6E: Elastography and Ultra sonography of 500.
Liver size: 1.8cm. Elastographicscore(pKa-2.3)

Effect on Histopathology on Liver Fibrosis

The normal group's liver tissues were determined to be structurally and morphologically normal. Vacuoles and edoema were seen in the hepatocytes of Cisplatin-treated rats, as was a high level of neutrophil infiltration. When L-carnitine was used at all levels, edoema and scarring were reduced, as seen in Figure 7.

DISCUSSION

Cisplatin-induced liver fibrosis is the most commonly used model for inducing obstructive cholestatic disease in mice and rats. When the biliary ducts become inflamed, that may lead to cirrhosis. Acute or irreversible liver damage may be the result, depending on how long the obstruction has been there.[22-23] Several studies modeled the effects of the drug on fibrosis and cirrhosis. It is caused by direct damage to the biliary epithelial cells, an immune response that results in mononuclear cell infiltration, and inflammation of the periductal region.[24] According to this study, L-carnitine has been shown to reduce Cisplatin-induced liver fibrosis in laboratory rats. Cisplatin was administered in high dosages of 3 mg/kg to induce liver fibrosis. The body weight of rats given cisplatin was lower, whereas rats given L-carnitine had a higher weight. Rats treated with Cisplatin had a rise in liver weight, but rats treated with L-carnitine had no change in liver weight. After secretory failure, toxic biliary chemicals might cause secondary adaptive alterations in hepatocytes to decrease their harmful effects.[25] Serum ALT, AST, TB, and HP levels were increased by the time the investigation was completed. Rats given L-carnitine had normal levels of all of these when compared to rats who didn't get it. Previous studies have shown that Cisplatin-induced hepatic oxidative stress causes hepatic oxidative stress. Our Cisplatin model exhibits oxidative stress and a decrease in GSH depletion, as well as an

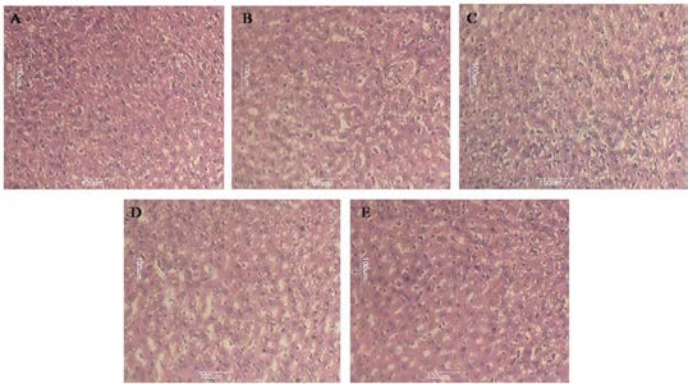

Figure 7: Effect of L-Carnitine on histopathology on liver fibrosis (A: Normal; B: Control; C: C100; D: C300; E: C500).

increase in the formation of lipid peroxides due to the accumulation of bile acids.[26] Cisplatin-induced plasma membrane damage may be increased by the detergent action and cytotoxicity of remaining bile salts, which may contribute to the time-dependent depletion of hepatic reduced GSH due to a lack of adequate reactive oxygen species scavengers. When rats are given L-carnitine, oxidative damage is reversed. According to the findings of this research, L-carnitine prevents Cisplatin-induced liver fibrosis in rats by normalizing biochemical markers, maintaining antioxidant enzyme and cytokine levels, and shielding liver tissue from injury. In future investigations, we plan to use a cell line to investigate the mechanism through which L-carnitine protects against liver fibrosis. Antifibrotic medication effectiveness and healthcare utilization can only be evaluated using a few imaging modalities that have just become accessible. The major goal of this study is to evaluate how effectively sonoelastography-MRI can detect liver fibrosis. Shear wave patterns were bigger in Cisplatin-treated mice, but there was a big drop in L-carnitine-treated animals.

CONCLUSION

In rats with liver fibrosis, L-carnitine exerts a protective effect. It lowers oxidative and nitrosative stress levels, as well as the quantity of pro-inflammatory cytokines produced. We conclude that additional study is needed to determine the involvement of L-carnitine in liver damage because Cisplatin lowered the MRI score in the rats.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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