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Amelioration of Moxifloxacin-Induced Hepatotoxicity in Rats by Vitamin C and L-Carnitine

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Abstract
Background: Moxifloxacin, a widely used fluoroquinolone antibiotic effective against a range of bacterial infections, has been associated with potential hepatotoxicity, a significant clinical concern that can limit its use. The underlying mechanism is strongly linked to oxidative stress. This study investigates the ameliorative effects of two well-known antioxidants, Vitamin C and L-Carnitine, against moxifloxacin-induced liver damage in adult male albino rats, aiming to identify potential and accessible strategies to mitigate these adverse effects. Methods: Forty adult male albino rats were systematically divided into four experimental groups (n=10): a control group receiving normal saline, a group receiving moxifloxacin (80 mg/kg), a group receiving moxifloxacin with Vitamin C (500 mg/kg), and a group receiving moxifloxacin with L-Carnitine (600 mg/kg). The treatments were administered daily for a period of 30 days. Finally, at the end of the study, the quantitative measurement of serum levels of major liver enzymes (Aspartate Aminotransferase - AST, Alanine Aminotransferase - ALT, Alkaline Phosphatase - ALP) and total serum bilirubin (TSB) was done. Liver tissues were also excised, processed, and subjected to close examination of the histopathological changes with attention being put to the degree of tissue cellular and architectural damage. Results: The moxifloxacin-treated group showed a statistically significant ($p \leq 0.05$) and marked increase in serum AST, ALT, ALP, and TSB levels compared to the healthy control group, indicating substantial hepatocellular injury. The biochemical observation was further confirmed by histopathological studies, which showed severe tissue damage of the liver, which involved massive cellular degeneration, hydrosis, focal necrosis and a noticeable inflammatory cellular infiltration in the portal and parenchymal regions. Concomitant administration of Vitamin C or L-Carnitine with moxifloxacin had a significant effect in reducing these high liver enzyme levels and considerably reducing the histopathological damage observed in the liver tissues leaving a far more normal hepatic architecture with considerably fewer inflammations and necroses. Conclusion: Moxifloxacin causes serious hepatotoxicity that is dose-dependent and likely caused by oxidative stress that damages cell integrity and cellular functions. The protective effect of strong antioxidants such as L-Carnitine and Vitamin C administered together is shown to have a considerable and clinically significant protective ability against this harm. These results also indicate a high possibility of their application as a useful adjuvant therapy to counteract the negative hepatic activity of moxifloxacin thus improving the safety of this valuable antibiotic in its clinical administration.

Keywords: Moxifloxacin, Hepatotoxicity, Oxidative Stress, Vitamin C, L-Carnitine

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Introduction
Moxifloxacin is a fourth-generation fluoroquinolone antibiotic that plays an important role in the modern world as it has a wide spectrum of action against different Gram-positive and Gram-negative bacterial pathogens (1). This renders it useful in the management of various ailments, such as community-acquired pneumonia, skin infections, and infected urinary tract that is complicated (2). Although it is effective clinically, there has been a mounting evidence of its ability to cause organ toxicity and liver is one of the major targets (3). Mechanism of this hepatotoxicity is thought to occur because of the production of excess reactive oxygen species (ROS), including superoxide anions as well as hydroxyl radicals, and results in a condition of a severe oxidative stress (4). This imbalance overloads the endogenous antioxidant system of the cell leading to cascade damage of cellular components such as lipids (lipid peroxidation) and structural proteins, and nuclear DNA leading to dysfunction and necrosis of cells (5).

In a bid to reverse this drug induced toxicity, much attention has been given to the therapeutic value of antioxidants (6). Vitamin C (ascorbic acid) is a potent water-soluble antioxidant, which has a fundamental role in the protection of oxidative damages in cells through the direct scavenging of free radicals as well as the restoration of other antioxidants such as Vitamin E (7, 8). It is a very good scavenger of aqueous ROS due to its capacity to donate electrons and hence inhibits the formation of destructive chain reactions (9). Another significant endogenous molecule is L-Carnitine, which is, first of all, a compound that is indispensable in the transportation of long-chain fatty acids to the mitochondria, where they undergo β-oxidation and further energy conversion (10). In addition to this metabolic action, it was also indicated to have a strong antioxidant effect that inhibits cell injury, especially in stabilising membranes in the mitochondrion, so that the leakage of electrons to produce ROS is inhibited (11). While the hepatotoxic risk of moxifloxacin is known, effective strategies to mitigate it clinically are not well-established. Therefore, this study aims to test the hypothesis that co-administering the antioxidants Vitamin C or L-Carnitine can ameliorate moxifloxacin-induced hepatotoxicity in a rat model, offering

a basis for safer therapeutic protocols.

Materials and Methods

This experimental study was conducted on 40 healthy adult male albino Wistar rats, weighing between 200-230 grams. The animals were procured from a certified breeder and were allowed to acclimatize for one week under standard laboratory conditions (22-25°C, 55±5% humidity, 12-hour light/dark cycle) with free access to standard pellet feed and purified water ad libitum. The rats were then randomly divided into four groups of ten each, ensuring homogeneity of weight across the groups:

- **Group 1 (Control):** Received a normal diet and water and was administered physiological saline via oral gavage daily.
- **Group 2 (Moxifloxacin):** Received moxifloxacin, dissolved in distilled water, at a dose of 80 mg/kg body weight via oral gavage.
- **Group 3 (Moxifloxacin + Vitamin C):** Received moxifloxacin (80 mg/kg) and Vitamin C (500 mg/kg) concurrently via oral gavage.
- **Group 4 (Moxifloxacin + L-Carnitine):** Received moxifloxacin (80 mg/kg) and L-Carnitine (600 mg/kg) concurrently via oral gavage.

All treatments were administered daily for a total of 30 days. At the end of the experimental period, the animals were fasted overnight and then anesthetized. Blood samples were collected via cardiac puncture into plain tubes for biochemical analysis. Serum was separated by centrifugation at 3000 rpm for 15 minutes and analyzed for liver function markers (AST, ALT, ALP, and TSB) using an automated clinical chemistry analyzer and standardized commercial kits. The animals were then humanely euthanized by cervical dislocation. Their livers were immediately dissected, washed with ice-cold saline, and a portion was fixed in 10% neutral buffered formalin for 48 hours. The fixed tissues were then processed through an ascending series of ethanol, cleared in xylene, and embedded in paraffin wax. Thin sections (5 µm) were cut using a rotary microtome, mounted on glass slides, and stained with standard Hematoxylin and Eosin (H&E) staining techniques for detailed histopathological evaluation under a light microscope.

Results

Biochemical Findings

The administration of moxifloxacin alone (G1) led to a significant and sharp increase in the serum levels of AST, ALT, ALP, and TSB when compared to the control group, as detailed in Table 1. These results are clear biochemical indicators of compromised hepatocellular integrity and cholestatic liver damage. Co-administration of either Vitamin C (G2) or L-Carnitine (G3) resulted in a significant and dramatic reduction in the serum levels of these liver enzymes, bringing them much closer to the normal physiological values observed in the control group.

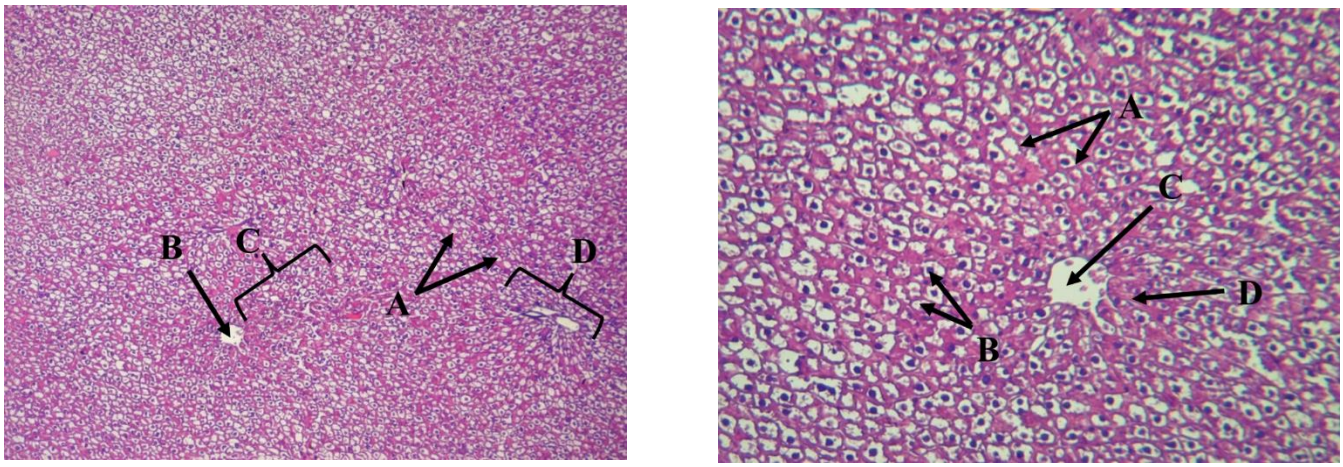
Table 1: Changes in serum liver enzymes and bilirubin levels in different treatment groups. Values are expressed as Mean ± Standard Error. G1 showed a significant ($p \leq 0.05$) increase compared to Control. G2 and G3 showed a significant decrease compared to G1.

Group	TSB (mg/dl)	AST (GOT) (IU/L)	ALT (GPT) (IU/L)	ALP (IU/L)
Control	0.060 ± 0.01	122.00 ± 11.20	34.50 ± 3.40	311.00 ± 9.80
G1 (Moxifloxacin)	0.320 ± 0.07	335.00 ± 28.00	78.50 ± 7.90	402.00 ± 14.50
G2 (Moxi + Vit C)	0.125 ± 0.04	185.00 ± 19.80	50.20 ± 5.50	292.00 ± 13.00
G3 (Moxi + L-Carnitine)	0.215 ± 0.06	252.00 ± 20.50	62.30 ± 6.40	328.00 ± 17.20

Histopathological Findings

The histopathological analysis of liver tissues provided a visual correlation to the biochemical findings, with normal architecture as described by Gartner & Hiatt (2013) (12) and Mescher (2018) (13) serving as a baseline.

Control Group: Examination of the control group's liver tissue revealed a normal hepatic architecture. The lobules were well-defined with a central vein and radiating cords of polygonal hepatocytes. These cells displayed distinct, centrally located nuclei and intact cytoplasm. The sinusoids between the hepatic cords were clearly visible and lined by endothelial and Kupffer cells, reflecting a healthy, physiological state (Figures 1).



Figures 1: Histology of normal liver tissue from the control group. (Left panel, 40X H&E stain) shows the overall hepatic architecture, including hepatocytes (A), a central vein (B), hepatic cords (C), and a portal area (D). (Right panel, 100X H&E stain) provides a higher magnification view, detailing the polygonal hepatocytes (A) with their central nuclei (B), the central vein (C), and the arrangement of hepatic cords (D).

Moxifloxacin-Treated Group: In stark contrast, the administration of moxifloxacin alone resulted in severe hepatic injury. The normal lobular architecture was distorted, characterized by extensive hepatocyte degeneration, diffuse cytoplasmic vacuolation (hydropic degeneration), and multiple foci of coagulative necrosis (Figure 2). There was significant congestion in blood vessels, marked dilation of the central vein and sinusoidal spaces, and fibrosis (Figures 3). At higher magnification, hepatocytes showed signs of severe damage, including fatty changes, hemorrhage, and pyknotic nuclei (Figure 4), confirming the profound hepatotoxic effect of the drug.

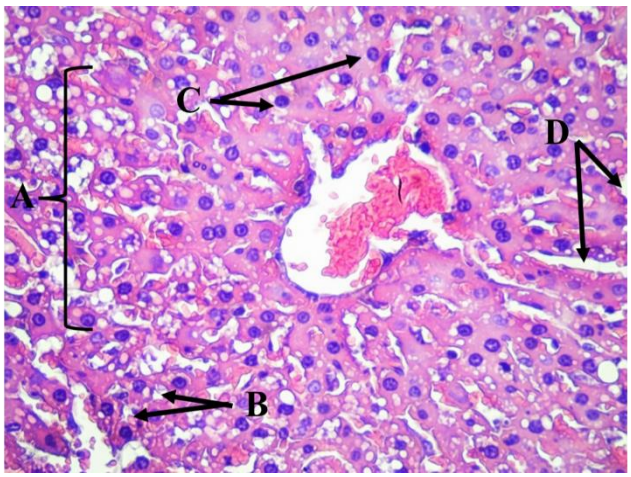
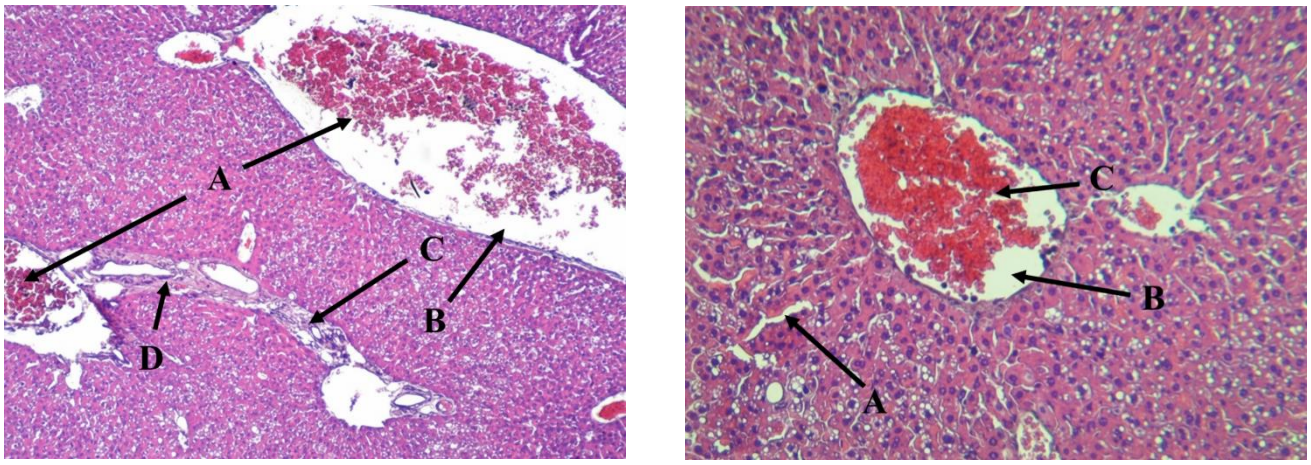


Figure 2: Liver of adult male rats affected with moxifloxacin showed high destructurization of Liver tissue (A), necrosis of hepatocytes (B), high pyknotic hepatocytes (C), high dilation of sinusoids (D) (H&E 100x).



Figures 3: Histopathological changes in the liver of rats treated with moxifloxacin (80 mg/kg). (Left panel, 40X H&E stain) shows widespread tissue destruction, characterized by vascular congestion (A), severe dilation of the central vein (B), infiltration of lymphocytes (C), and fibrosis. (Right panel, 100X H&E stain) offers a closer view, detailing the dilation of sinusoidal spaces (A), a dilated central vein (B), and high levels of congestion in blood vessels (C).

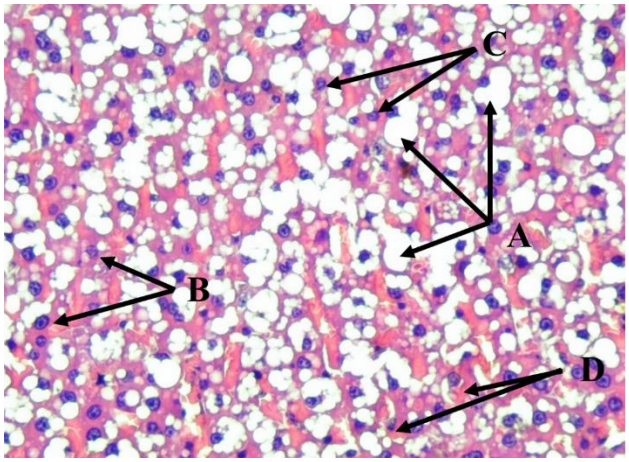
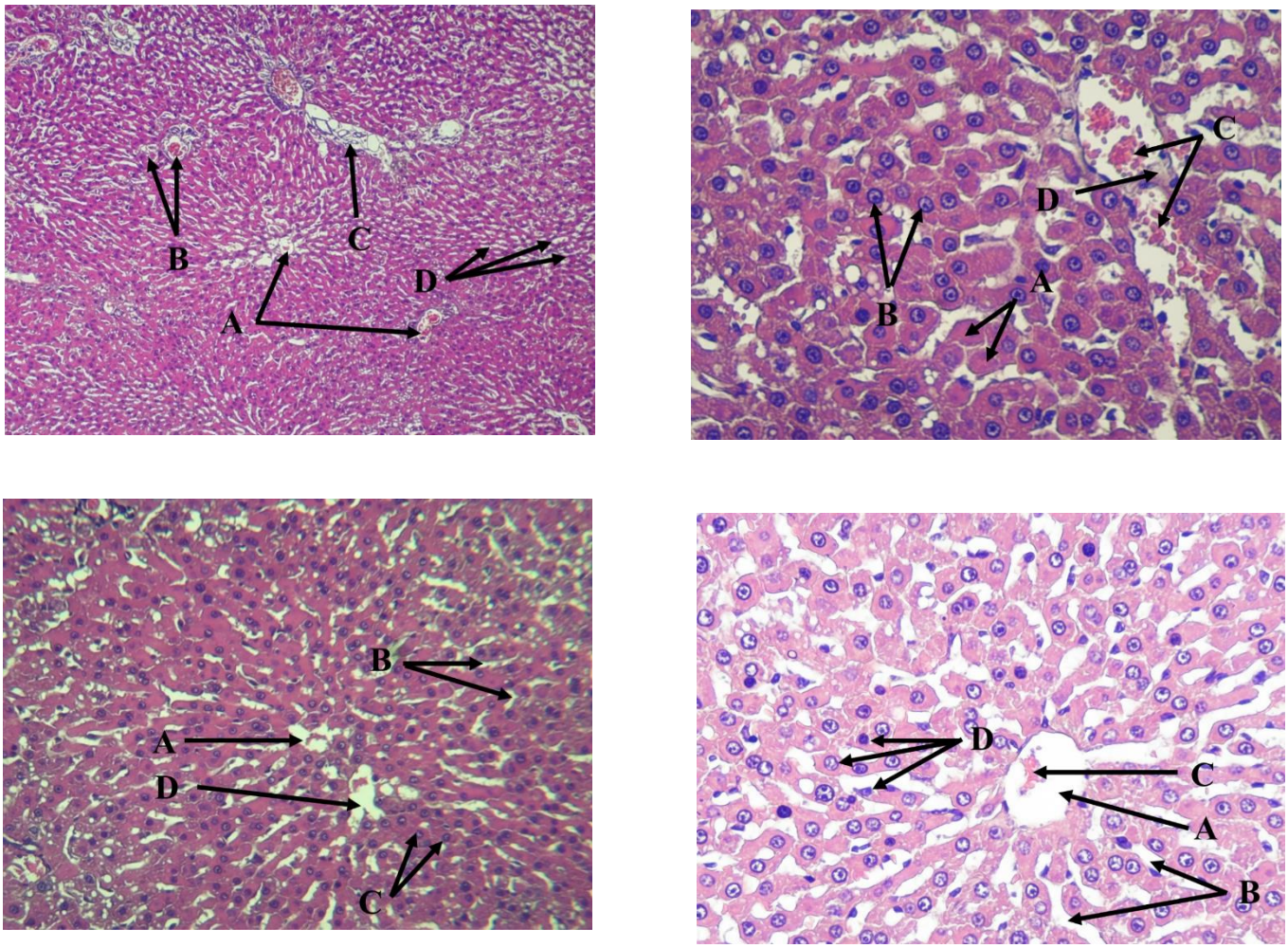


Figure 4: Liver of adult male rats affected with (moxifloxacin 80 mg/kg) showed very fatty cells (A), haemorrhage (B), pyknotic nucleus (C), & cloudy degeneration (D) (H&E 400x).

Antioxidant Co-treated Groups: The groups that received either Vitamin C or L-Carnitine in addition to moxifloxacin showed a remarkable improvement in liver architecture. In the Vitamin C group, there was a marked reduction in the signs of cellular damage, with less congestion and dilation of the central vein and sinusoids, and a significant decrease in inflammatory infiltration (Figures 5). Similarly, the L-Carnitine group exhibited a significant protective effect, with less hepatocyte degeneration and congestion, and a notable increase in the population of normal-appearing hepatocytes (Figures 6). The degree of inflammation and necrosis was minimal in both antioxidant-treated groups, and the lobular structure was largely preserved, indicating a strong and effective protective action against the hepatotoxic insult induced by moxifloxacin.

Figures 5: Protective effect of Vitamin C (500 mg/kg) on moxifloxacin-induced liver damage. (Left panel, 40X H&E stain) shows a significant reduction in overall tissue damage, with less dilation of the central vein (A), reduced vascular congestion (B), minimal lymphocyte infiltration (C), and less dilation of sinusoids (D). (Right panel, 400X H&E stain) provides a high-magnification view, demonstrating less hepatocyte degeneration (A), a higher number of normal-appearing hepatocytes (B), and reduced congestion (C)

and dilation (D) in the blood vessels.



Figures 6: Protective effect of L-Carnitine (600 mg/kg) on moxifloxacin-induced liver damage. (Left panel, 100X H&E stain) shows a marked improvement in the liver's overall structure, with reduced dilation of the central vein (A) and sinusoids (B), less hepatocyte degeneration (C), and minimal congestion (D). (Right panel, 400X H&E stain) provides a detailed view at higher magnification, confirming the preservation of the central vein (A) and sinusoids (B), a significant reduction in congestion (C), and a notable increase in the population of healthy, normal-appearing hepatocytes (D).

Discussion

The results of this study clearly and unequivocally demonstrate that moxifloxacin, at the administered dose and duration, can induce significant hepatotoxicity in rats. It is also consistent with the works by Akinyemi et al. (2015) (14) and Andriole (2005) (15), who also reported that the administration of moxifloxacin in rats caused material increases in plasma ALT, AST, ALP, and bilirubin and therefore, the dysfunction of the liver. The high concentration of intracellular liver enzymes (AST, ALT) in the blood is a direct and measurable result of the damage done to the hepatocyte plasma membranes making them lose their integrity and thus their cytoplasmic contents leak (16). The elevation of ALP and TSB further indicates the presence of an aspect of cholestasis, or bile impaired flow. These histopathological results, including necrosis, inflammation, and steatosis (Figures 2 and 3) also confirm the degree and gravity of cellular tissue damage.

The great protective effect of Vitamin C and L-Carnitine may be regarded as a reliable outcome of the strong and versatile antioxidant effect, and El-Maddawy and El-Sayed (2018) (17) also find similar evidence of the phenomenon in a similar study (17). Inhibiting the harmful radicals and decreasing the overall load of the oxidative stress, these compounds can protect the liver cells against the harmful cascade of the moxifloxacin (18). Vitamin C is a primary water-soluble antioxidant, which is known to directly counteract ROS in the cytosol and extracellular space, hence preventing the onset of lipid peroxidation, which is an essential pathway in membrane damage (7, 19). L-Carnitine, by its turn, is highly important in terms of preserving the health of mitochondria and their metabolism (20). Its antioxidant effect has been attributed to its capacity to reverse moxifloxacin-induced hepatotoxicity (21). It enhances the correct transport and oxidation of fatty acids and prevents the loss of electrons out of the electron transport chain and

avoids the build-up of toxic lipid intermediates that may further increase cellular stress (22). The apparent changes in the biochemical markers (Table 1) and the liver histological structure of the liver (Figures 4 to 6) are a strong indicator that proves this mechanistic hypothesis. The clinical implication of these findings is significant, as it suggests that concurrent supplementation with safe and affordable antioxidants could be a viable strategy to enhance the safety of necessary antibiotic treatments (23).

Conclusion

Moxifloxacin administration can lead to significant, clinically relevant liver damage, characterized by both biochemical and structural abnormalities. The co-administration of powerful antioxidants like Vitamin C and L-Carnitine can effectively and substantially mitigate this hepatotoxicity by counteracting the underlying mechanism of oxidative stress. These findings strongly suggest that the use of these antioxidants could be a valuable and proactive strategy to reduce the adverse effects of moxifloxacin in clinical practice. Incorporating such protective agents into treatment regimens could potentially improve patient safety and tolerance, particularly during long-term or high-dose antibiotic therapy, thus preserving the utility of this important antibacterial agent.

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