RESEARCH ARTICLE

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The Ameliorative Effect of Vitamin C Against Clarithromycin-Induced Hepatotoxicity in Rats: The Role of Oxidative Stress, Inflammation, and the BAX/BCL-2/Caspase-3 and Beclin-1/LC3A Pathways

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The aim of the study was to investigate the protective effects of vitamin C (Vit C) against the toxic effects of clarithromycin (CLM) administration in rat liver. In the study, rat livers were examined in for liver enzymes, oxidative stress, apoptosis, autophagy, and inflammation. CLM was administered orally at a dose of 45 mg/kg for 7 days. Vitamin C was administered intraperitoneally (i.p.) at 100 mg/kg/day for 7 days. The findings showed that Vit C significantly reduced apoptotic markers, oxidative stress, liver enzymes, autophagic activity, and inflammation in response to CLM administration. In conclusion, the protective effect of Vit C against the toxic effects of CLM, which is widely used in both human and animal health, on the liver has been demonstrated.

Key Words: *Apoptosis, clarithromycin, hepatotoxicity, oxidative stress, vitamin C*

Sıçanlarda Klaritromisin Kaynaklı Hepatotoksiye Karşı C Vitamininin İyileştirici Etkisi: Oksidatif Stres, İnflamasyon, BAX/BCL-2/Kaspaz-3 ve Beklin-1/LC3A Yollarının Rolü

Bu çalışmanın amacı, sıçan karaciğerinde klaritromisin (CLM) uygulamasının toksik etkilerine karşı C vitamininin (Vit C) tedavi edici ve koruyucu etkilerini araştırmaktır. Çalışmada, sıçan karaciğerleri, karaciğer enzimleri, oksidatif stres, apoptoz, otofaji ve inflamasyon açısından incelenmiştir. CLM, 45 mg/kg dozda 7 gün boyunca oral yolla uygulandı. Vit C, 100 mg/kg/gün dozda intraperitoneal (i.p.) yol ile 7 gün boyunca uygulandı. Bulgular, Vit C'nin CLM uygulamasına yanıt olarak apoptoz belirteçlerini, oksidatif stresi, karaciğer enzimlerini, otofajik aktiviteyi ve inflamasyonu önemli ölçüde azalttığını göstermiştir. Sonuç olarak, hem insan hem de hayvan sağlığında yaygın olarak kullanılan CLM'nin karaciğer üzerindeki toksik etkilerine karşı Vit C'nin koruyucu etkisi gösterilmiştir.

Anahtar Kelimeler: *Apoptoz, klaritromisin, hepatotoksisite, oksidatif stres, C vitamini*

Introduction

Clarithromycin (CLM) is a broad-spectrum macrolide antibiotic developed in 1980 and approved for medical use in 1990. CLM is used in various bacterial infections such as streptococcal throat infection Lyme disease, pneumonia, *Helicobacter pylori* infection, and skin infections. The drug can be administered orally in tablet or liquid form or intravenously. CLM is a macrolide antibiotic. It exerts its effect by inhibiting the protein synthesis of bacteria (1). In addition to its common side effects, CLM has been reported to negatively affect the liver. Studies have shown that it increases liver enzymes and can lead to acute liver failure (2, 3).

Vit C is an essential water-soluble micronutrient with numerous effects, including maintaining redox balance, collagen biosynthesis, neurotransmitter formation, and immune defense (4). It is a very powerful antioxidant. It protects biomolecules from oxidative damage and contributes to enzymatic regulation and iron homeostasis (5). The recommended daily intake of Vit C for a healthy adult human is 500 mg (5).

Previously, the effects of Vit C on organs such as the liver and kidneys were investigated, and it was shown to reduce oxidative stress, repair biochemical changes, and almost restore metabolic regulation (6, 7).

The main objective of this study is to investigate the liver-protective and preventive effects of Vit C against the toxic effects of CLM, a macrolide antibiotic widely used in human and animal health that has adverse effects on the liver.

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Materials and Methods

Research and Publication Ethics: Approval was obtained from the Necmettin Erbakan University Local Ethics Committee for Animal Experiments. Approval date and number: 27.11.2025, 2025-103. All experimental procedures in our study were carried out in accordance with European Directive 2010\63\AB. The study was carried out in accordance with ARRIVE guidelines.

Chemicals: The drugs used in the study were CLM (Klamer®, 500 mg) from Atabay (İstanbul, Turkey) and Vit C (Maxivit-C®, 200 mg ascorbic acid per mL of 100 mL solution) from Arion (İstanbul, Turkey). The CLM dose was determined according to the methodology applied by Wen (8), while the Vit C dosage was established according to the study by Ayyıldız (9).

Experimental Procedures: In this study, 28 Wistar albino rats were used. The rats weighed 225-255 g and were 11-13 weeks old. The rats were obtained from Necmettin Erbakan University KONUDAM Experimental Medicine Application and Research Center (Konya, Turkey).

Rats were weighed, and four balanced groups were formed (n=7)

1. Control: A solution of normal saline was orally administered once daily for 7 days.

2. Clarithromycin (CLM): It was administered orally once daily for 7 days at a dose of 45 mg/kg, dissolved in 2 ml of distilled water.

3. Vit C (Vit C): It was administered once a day by i.p. route at a dose of 100 mg/kg/day for 7 days.

4. Clarithromycin+Vit C (CLM+Vit C): CLM administered orally once daily for 7 days at a dose of 45 mg/kg, dissolved in 2 mL of distilled water and Vit C was administered once a day by i.p. route at a dose of 100 mg/kg/day for 7 days. CLM administered first, followed Vit C treatment.

CLM was administered orally to rats once daily for 7 days. Vit C was administered i.p. once daily for 7 days. The experiment was terminated on day 8. The procedures and substance administrations were carried out according to predetermined protocols (8, 9).

The rats used in the experiment were sacrificed by decapitation under sevoflurane anesthesia (100% Sevorane fluid) 24 h after their last treatment. Blood samples were collected in tubes without anticoagulant and centrifuged at 3000 xg for 10 minutes at 4ºC to extract the serum, which was then separated for ALT and AST determination. The livers were rapidly removed from the animals and stored at -80°C for biochemical analysis.

Liver Function Tests: To assess hepatic function, serum levels of AST and ALT were measured. All analyses were carried out using commercial assay kits, following the manufacturer's instructions. Serum samples obtained from blood were prepared in the laboratory under necessary precautions, and enzyme activities were measured using spectrophotometric methods.

Lipid Peroxidation and Antioxidant Analyses in Liver Tissue: Liver tissue was homogenized in 1.15% potassium chloride solution in a homogenizer (TissueLyser II, Qiagen, Netherlands) to obtain homogenate. The protein content of liver tissue was evaluated using the methods of Lowry et al. (10), malondialdehyde (MDA) level by Placer et al. (11), glutathione (GSH) level by Sedlak and Lindsay (12), catalase (CAT) activity by Aebi (13), superoxide dismutase (SOD) activity by Sun et al. (14), and glutathione peroxidase (GPx) activity by Lawrence and Burk (15).

Real Time – Polymerase Chain Reaction (RT-PCR): RNA was obtained from rat liver tissues. (QIAzol Lysis Reagent 79306, QIAGEN) cDNA was synthesized from the RNA samples (OneScript Plus cDNA Synthesis Kit, ABM, G236, Richmond, Canada). The obtained cDNA was used to determine the mRNA levels of cysteine-aspartic protease-3 (Caspase-3), BCL2 Associated X (Bax), B-cell lymphoma 2 (Bcl-2), nuclear factor kappa B (NF-κB) and interleukin 1 beta (IL-1β), Beclin 1, Light Chain 3 Alpha (LC3A) genes. The primer sequences are given in Table 1. (16) using the $2^{\wedge-\Delta\Delta CT}$ method, normalized to β-Actin (17).

Table 1. Primer sequences

Gene	Sequences (5'-3')
NF-κB	F: AGTCCCGCCCCTTCTAAAAC
	R: CAATGGCCTCTGTGTAGCCC
Bcl-2	F: GACTTTGCAGAGATGTCCAG
	R: TCAGGTACTCAGTCATCCAC
Caspase-3	F: ACTGGAATGTCAGCTCGCAA
	R: GCAGTAGTCGCCTCTGAAGA
Bax	F: TTTCATCCAGGATCGAGCAG
	R: AATCATCCTCTGCAGCTCCA
LC3A	F: GACCATGTTAACATGAGCGA
	R: CCTGTTCATAGATGTCAGCG
Beclin-1	F: TCTCGTCAAGGCGTCACTTC
	R: CCATTCTTTAGGCCCCGACG
β-Actin	F: CAGCCTTCCTTCTTGGGTATG
	R: AGCTCAGTAACAGTCCGCCT
IL-1β	F: ATGGCAACTGTCCCTGAACT
	R: AGTGACACTGCCTTCCTGAA

Statistical Analysis: SPSS 26.0 software was used to analyze the data obtained in the study (SPSS Inc., Chicago, USA). Shapiro-Wilk and Kolmogorov-Smirnov normality tests and QQ plots were used to assess the distribution of variables. Homogeneity of variance was assessed using Brown-Forsythe and Bartlett tests. For data satisfying the assumptions of normal distribution and homogeneity of variance, one-way analysis of variance (One-Way ANOVA) and Tukey

multiple comparison test were used. Statistically significant data are presented as mean ± standard deviation (SD). Differences were considered statistically significant at the $p<0.05$, $p<0.01$, and $p<0.001$ levels.

Results

Results of Liver Function Test: Compared to the control group, CLM administration increased ALT and AST levels ($p<0.001$). Compared to the CLM group, CLM+Vit C supplementation resulted in a significant decrease in both ALT ($p<0.01$) and AST ($p<0.001$) values. Compared to the control group, the difference in CLM+Vit C administered group was highly statistically significant ($p<0.001$). In conclusion, Vit C treatment reduced the negative effects of CLM (Figure 1).

Effects of CLM and Vit C on Lipid peroxidation and Activity of Antioxidants in Liver Tissues: When the CLM-treated group was compared with the Control Group, a significant increase in MDA levels was observed. Simultaneously, a decrease was observed in antioxidant GPx, SOD, GSH, and CAT activities ($p<0.001$). On the other hand, when the CLM+Vit C group was compared with the CLM group, a significant decrease in MDA levels was observed ($p<0.001$), while a significant increase was observed in CAT, SOD, GPx, and GSH levels ($p<0.001$). Compared to the control group, CLM+Vit C administered MDA levels increased significantly (p<0.001), while GSH, GPx, SOD, and CAT levels decreased significantly ($p<0.001$) (Figure 2).

Inflammatory Parameters in Liver Tissue: NF-κB and IL-1β parameters were examined to measure the degree of inflammation. NF-κB and IL-1β levels were higher in the CLM-treated group compared to the control group ($p<0.001$). The group administered with CLM + Vit C showed lower levels of NF-κB and IL-1β compared to the CLM group ($p<0.01$). Compared to the control group, CLM+Vit C administered NF-κB and IL-1β were significantly higher ($p<0.001$) (Figure 3).

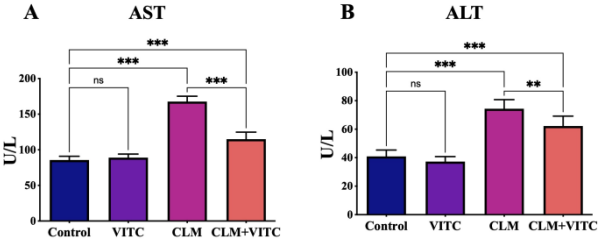

Figure 1. Effects of clarithromycin (CLM) and Vit C (Vit C) applications on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in rat liver tissue. Values are given as mean ± standard deviation. Statistical signifcance (ns: not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$).

Apoptosis in Liver Tissue: To determine apoptotic damage, Caspase-3, Bax, and BCL-2 levels were examined in liver tissues. RT-PCR was used to analyze mRNA transcription levels. In the CLM group, compared to the CLM+Vit C group, an increase in apoptotic Caspase-3 and Bax levels was observed ($p<0.001$), while a significant decrease in anti-apoptotic Bcl-2 levels was observed ($p<0.05$). Compared to the control group, the group treated with CLM+Vit C had higher levels of Caspase-3 ($p<0.001$) and Bax ($p<0.01$) and lower level of Bcl-2 ($p<0.01$) (Figure 4).

Autophagy: Beclin-1 and Light chain 3 alpha (LC3A) markers were measured to assess autophagic damage. mRNA levels were determined by RT-PCR. In the CLM group, autophagic markers increased compared to the control group ($p<0.001$). In the CLM+Vit C group, autophagic activity showed a significant decrease in both markers compared to the CLM group ($p<0.01$ and $p<0.05$, respectively). Compared to the control group, the group treated with CLM+Vit C had significantly higher levels of Beclin-1 and LC3A ($p<0.001$) (Figure 5).

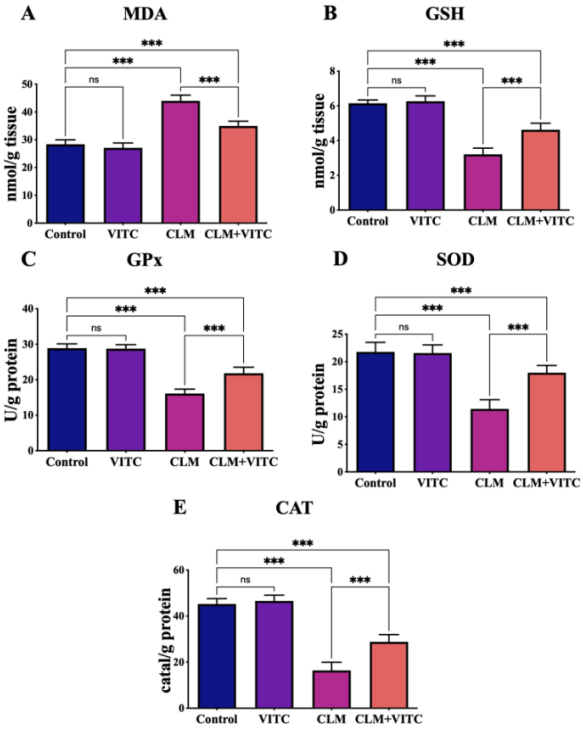

Figure 2. Effects of clarithromycin (CLM) and Vit C (Vit C) administrations on malondialdehyde (MDA) and glutathione (GSH) levels and superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activity in liver tissue of rats. Values are given as mean ± standard deviation. Statistical signifcance (ns: not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$).

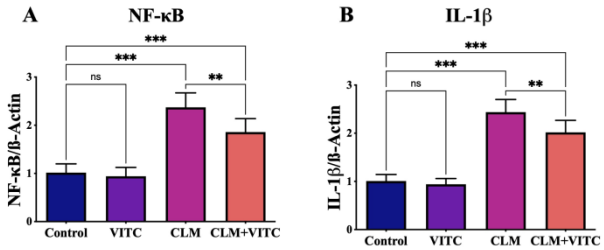

Figure 3. Effects of clarithromycin (CLM) and Vit C (Vit C) applications on nuclear factor kappa B (NF-κB) and interleukin 1 beta (IL-1β) levels in rat liver tissue. Values are given as mean ± standard deviation. (ns: not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$).

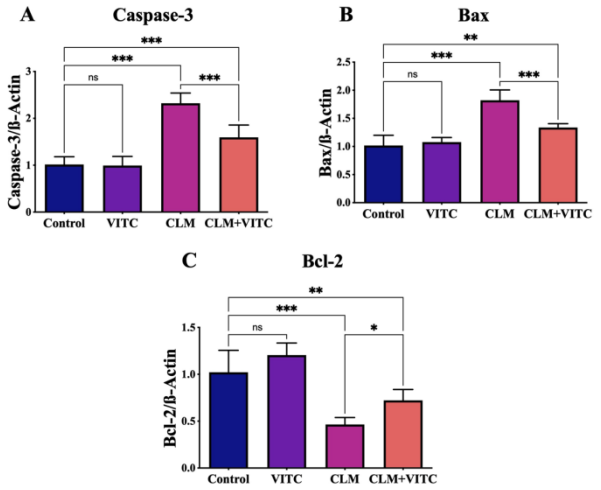

Figure 4. Effects of clarithromycin (CLM) and Vit C (Vit C) administrations on cysteine-aspartic proteases-3 (Caspase-3), BCL2 associated X (Bax) and B-cell lymphoma 2 (Bcl-2) mRNA transcription levels in liver tissue of rats. Values are given as mean ± standard deviation. Statistical signifcance (ns: not significant, **p*<0.05, ***p*< 0.01, ****p*<0.001).

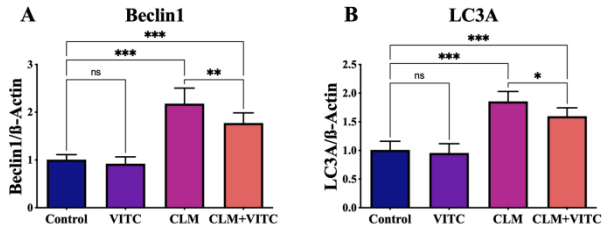

Figure 5. Effects of clarithromycin (CLM) and Vit C (Vit C) administrations on Beclin-1 and Light Chain 3 Alpha (LC3A) mRNA transcription levels in liver tissue of rats. Values are given as mean ± standard deviation. Statistical signifcance (ns: not significant, **p*<0.05, ***p*<0.01, ****p*<0.001).

Discussion

According to the results of the study, Vit C treatment mitigated existing liver damage caused by CLM application by regulating elevated liver enzymes, oxidative stress, apoptosis, and autophagy damage pathways.

Free radicals cause oxidative stress, which can lead to tissue damage (18, 19). Increasing the production of reactive oxygen species (ROS) increases the oxidant capacity in parallel (20). Conversely, antioxidants found in the cell can neutralize free radicals, thus keeping ROS levels in balance (21, 22). Consequently, if the antioxidant capacity decreases while the ROS level increases in the cell, oxidative stress is triggered (23, 24). When oxidative stress occurs, it can damage the cell's lipid structure, protein content, and DNA (25). Lipids in the cell membrane are directly affected by increased ROS, and MDA levels increase simultaneously (26). Among antioxidant enzymes, SOD converts superoxide, an oxidative stress product, into hydrogen peroxide (H_2O_2). CAT breaks down H_2O_2 into oxygen and water, while GPx is effective in neutralizing both cytotoxic lipid peroxides and H_2O_2. The non-enzymatic antioxidant GSH reduces high ROS levels (27, 28). It has been observed that CLM application increases MDA level, decreases CAT, GPx, SOD, and GSH levels, and consequently increases oxidative stress (29). Vit C, on the other hand, has the opposite effect, reducing oxidative stress.

Increased ROS levels increase NF-κB, which triggers inflammation, and IL-1β, a cytokine that NF-κB stimulates (30, 31). Therefore, lowering NF-κB and the inflammatory cytokines it stimulates, L-1β and IL-6 levels, can reduce the inflammatory process (32). In this study, evaluated using rat liver, CLM administration increased NF-κB and IL-1β levels in tissues and increased inflammatory damage. Vit C, on the other hand, reduced all these effects of CLM.

Apoptosis is programmed cell death (33). Apoptosis typically occurs in healthy cells following cellular stress or injury (16). It is effective in removing cells damaged by increased free radical production and thus from the environment, and this occurs through the activation of caspases (34). P53, which plays a critical role in cell death caused by DNA damage, increases over time when DNA is damaged, phosphorylation occurs, and excessive proapoptotic reactions are triggered (35). The mitochondrial pathway plays a critical role in apoptosis processes. When the level of Bax, a pro-apoptotic protein, exceeds the levels of anti-apoptotic proteins, Bax translocates to the cytoplasm, thereby triggering apoptotic caspase activation (36, 37). This study showed that CLM administration caused damage to rat liver tissues by increasing apoptotic factors and decreasing anti-apoptotic factors. CLM+Vit C administration reversed this situation. Vit C treatment showed protective properties against apoptotic damage caused by CLM administration in liver tissues. Autophagy is a cell-to-cell degradation process induced by Beclin-1 and LC3A, involving the breakdown of unnecessary or damaged organelles and proteins within cells via lysosomes (38). Autophagy is also induced by oxidative stress (39). An excessive increase in autophagy levels causes tissues and organs to lose their function (40). Therefore, autophagy plays a crucial role in adaptation and cellular immunity (41). Vit C, on the other hand, has shown protective properties against autophagic damage by reducing CLM-derived LC3A and Beclin 1 levels (42). The CLM application triggers autophagy by increasing the amount of free Beclin-1 through phosphorylated Bcl-2. This, in turn, causes CLM to influence autophagy as a “damaging process” (43).

The liver is a vital organ with a crucial function: removing toxic substances from the body (44). AST and ALT enzymes are liver biomarkers. High levels indicate both disruption of the integrity of the cell membranes of liver tissue and liver damage. Increased serum AST and ALT enzyme levels occur as a result of the leakage of these enzymes into the blood due to the disruption of membrane integrity following damage or necrosis of hepatocytes (24). In the present study, increased serum AST and ALT levels with CLM administration indicate that CLM causes toxic damage to liver tissue. A decrease in serum AST and ALT levels was observed

with CLM+Vit C administration. Thus, Vit C administration had a protective effect against the toxic effects of CLM on the liver.

This study presents clinically significant potential for Vit C treatment in CLM-induced hepatotoxicity. Pathological processes caused by CLM led to severe damage in rat liver. Vit C administration mitigated these negative changes (45). In medical practice, the application of Vit C in the treatment of serious damages such as hepatotoxicity stands out as an effective method that accelerates tissue healing by reducing oxidative stress, inflammation, and apoptosis. Our study has demonstrated the supportive effects of Vit C on tissue healing through its protective effects on cellular proliferation, apoptotic damage, and inflammation (26), The findings of the study suggest that Vit C can be incorporated into medical treatment protocols and may be an adjunct treatment option, particularly in acute conditions such as liver damage.

Consequently, based on the findings of the current study, it was observed that CLM causes toxic damage in rat liver tissues by activating oxidative stress, apoptosis, inflammation, and autophagic damage pathways. In contrast, Vit C treatment showed protective properties against CLM toxic damage by reducing the effects of all these damage pathways. Vitamin C achieved this protective effect by maintaining the Bax/Bcl-2 balance.

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