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Hepatoprotective Effects of Coenzyme Q10 against Amoxiclav-induced Hepatotoxicity in the Rat Model

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ABSTRACT

Aims Amoxiclav antibiotic is a commonly prescribed medication for many medical situations. One of the side effects of amoxiclav is hepatotoxicity. Coenzyme Q10, as a potent anti-oxidant, can play a beneficial role in reducing various drug-induced hepatotoxicity. The present study aimed to evaluate the hepatoprotective effects of coenzyme Q10 against amoxiclav-induced hepatotoxicity in the rat model.

Materials & Methods 24 male albino rats weighing 150-250g were randomly divided into four groups of six animals. The control group was given normal saline; the amoxiclav group was given 30mg/Kg/day of amoxiclav orally for 30 days; In the amoxiclav and CoQ10 group, each animal was given orally 30mg/Kg of amoxiclav, and 100mg/Kg CoQ10 orally daily for 30 days; In CoQ10 group, each rat was given 100mg/Kg CoQ10 orally daily for 30 days. At the end of the experiment, the animals were anesthetized and then scarified to assess the serum liver enzymes, as well as liver tissue samples were obtained for histopathological study.

Findings Liver function parameters were significantly elevated in the animal group treated with amoxiclav, and hepatocellular necrosis and congestion were observed in histopathological examination. Concomitant treatment with CoQ10 and amoxiclav significantly reduced the liver enzymes and improved hepatocellular congestion and inflammation.

Conclusion CoQ10 is a potent anti-inflammatory and anti-oxidant agent that can be used to reduce amoxiclav-induced hepatotoxicity.

Keywords Amoxiclav; Coenzyme Q10; Liver; Toxicity; Adverse Effects; Rat

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Introduction

Amoxicillin-clavulanate (Amoxiclav) is one of the most common antimicrobial drugs worldwide. It is a combination of two different drugs: amoxicillin and clavulanic acid. Amoxicillin is a penicillin derivative and has similar activity against gram-positive and gram-negative bacteria. Furthermore, with the addition of clavulanic acid, include all beta-lactamase-producing strains of bacteria [1].

Amoxiclav is a beta-lactamase inhibitor that works by inhibition of bacterial growth of different types. It is widely prescribed for the treatment of certain bacterial infections of mild or moderate severity, is taken orally, and is well tolerated [2].

Amoxiclav is only available in oral formulations and, like most bactericidal antibiotics, needs to be administered at regularly scheduled intervals to minimize differences in the antimicrobial's peaks and troughs. This approach helps maintain consistent serum concentrations over the Minimum Inhibitory Concentration (MIC) needed to destroy the targeted organism effectively; this is generally accomplished by a twice or three times daily administration of the medication [3]. It is recommended to take this antimicrobial with food to enhance absorption and minimize any adverse gastrointestinal symptoms [4].

Amoxiclav is largely safe and well-tolerated in the general population, with the vast majority of adverse effects being only mild gastrointestinal symptoms [5]. Very rare side effects of amoxiclav include prolonged prothrombin time, vasculitis, thrombocytopenia, cholestatic jaundice, elevated serum alkaline phosphatase, hepatitis, and hepatotoxicity [6-8].

Although amoxiclav is an excellent antimicrobial, it is one of the most frequent causes of idiosyncratic drug-induced hepatic injury. Men are at increased risk when compared to women, as well as patients greater than 50 years of age. Other factors include genetic polymorphisms, HIV patients on antiretroviral therapy, or concomitant use of medications that influence the cytochrome P450 pathway. The time of symptom onset is generally 2 to 3 weeks after the initial dose but may occur more rapidly or even be delayed up to 12 weeks. Treatment involves immediate discontinuation of the offending agent and limiting the use of other hepatotoxic drugs [7-9].

One of the possible amoxiclav adverse reactions is liver toxicity achieved by oxidative stress that leads to either cholestatic jaundice or idiosyncratic drug-induced liver injury, which occurs irrelevant to the dose or concentration of the drug. Toxicity is manifested by increment in the levels of Alanine transaminase (ALT), Aspartate aminotransferase (AST), and bilirubin [10]. This liver toxicity can occur even after stopping the course of therapy and may take weeks to recover. It comprises nausea, vomiting, and abdominal pain together, with elevation in liver enzymes [11]. The mechanism of such injury is unknown but could be of immunological bases associated with the Human Leukocyte Antigen (HLA) class II allele [12].

Coenzyme Q10 (Ubiquinone) is a natural quinone, which is a fat-soluble material and simulates vitamins found in aerobic bacteria and most mammalian mitochondria. This compound is a 1,4-benzoquinone. The “Q” assigns the quinone group, and “10” assigns the number of isoprenyl groups in its structure [13]. It is an integral part of the electron transport chain and take place in aerobic respiration of the cell that makes energy in an ATP form so coenzyme Q10 is highly concentrated in liver, heart, brain, and kidney where energy is highly needed [14].

Coenzyme Q10 is commonly used as a dietary supplement and in many medical situations as adjuvant therapy since it has anti-inflammatory, anti-apoptotic, antiproliferative, and antioxidant properties and is considered a potent endogenous anti-oxidant [15]. This compound can play a beneficial role in various drug-induced hepatotoxicity as well as liver destruction due to metabolic disturbances [16]. Furthermore, it was found that CoQ10 could have neuroprotective effects due to its high level in the brain tissue [17].

Researchers have discovered several biological activities, including free radical-scavenger properties, hepatic injury lowering effects, and reduced endothelial cell impairments [18]. In many studies on animal models of hepatotoxicity, CoQ10 reduced the ammonia levels in the plasma and decreased the rate of the hepatic pathological insults progress. CoQ10 carries antioxidant, anti-inflammatory, and protective effects against mitochondrial reactive oxygen species over-release [19].

More studies are necessary to confirm the efficacy, therapeutic effects, side effects, and the exact dose of CoQ10. The proofing of the CoQ10 as a medication line for liver toxicity will have a huge impact on the patients waiting to receive liver transplantation by slowing the disease's progression, thereby saving lives and giving them a higher chance of survival [20].

Therefore, the present study aimed to evaluate the hepato-protective effects of coenzyme Q10 against amoxiclav-induced hepatotoxicity in the rat model.

Materials and Methods

Study design and animals

In this experimental study, 24 male albino rats weighing 150-250g were purchased in March 2021. They were randomly divided into four groups of six animals, which were kept in the animal house of the College of Pharmacy, Kerbala University, with open access to water and standard pellet food.

The animal groups were divided as follows:

1. Control group: This group was given only standard chow food and normal saline.
2. Amoxiclav group: This group was given 30mg/Kg/day of amoxiclav orally for 30 days [21].

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3. Amoxiclav and Coenzyme Q10 group: Each animal was given orally 30 mg/Kg of amoxiclav and 100 mg/Kg Coenzyme Q10 orally daily for 30 days [22].
4. Coenzyme Q10 group: Each rat in this group was given 100mg/Kg Coenzyme Q10 orally daily for 30 days.

Drug used in the study

6 mg of amoxiclav was dissolved in 1 ml of distilled water. 6 mg of amoxiclav was dissolved in 1ml of distilled water. Both drugs were given by gavage for 30 days. Animals were clinically assessed every day. At the end of the experimental period, the animals were anesthetized using chloroform and then scarified. Blood was collected by cardiac puncture for serum biochemical analysis, and liver tissue samples were obtained for histopathological study.

Liver function test parameters assessment method

Blood serum was separated to measure liver enzymes, and Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), and Total Serum Bilirubin (TSB) were assessed by spectrophotometric method.

Preparation of histopathological slides

The liver organ was isolated and preserved in 10% formalin for histological examination.

Statistical analysis

The results were presented as mean ± standard deviation. The difference in means between the control group and other experimental groups was analyzed using one-way Analysis of Variance (ANOVA) in SPSS 20 software.

Findings

The mean concentration of TBS was not significantly different between the studied groups. The mean concentration of ALP in the amoxiclav group was significantly higher compared to the control group, but in the other two experimental groups, no significant difference was observed compared to the control group. The mean concentration of ALT and AST enzymes was significantly higher in the amoxiclav group compared to the control group. In the amoxiclav+Q10 group, the ALT and AST values were significantly lower than the amoxiclav group but higher than the control group. However, no significant difference was observed between the coenzyme Q10 group and the control group (Table 1). The liver cross-section of the control group showed normal lobular and acini, including the central vein and portal tract radially that were arranged around it (Figure 1).

In Amoxiclav group, the liver section showed that there is significant congestion with the central lobular accumulation of bile, infiltration of inflammatory cells (neutrophils, lymphocytes, and eosinophils), degeneration in some hepatocytes, vacuolated cytoplasm, with spotty focal necrosis in parenchyma without fibrosis or edema (Figure 2).

In Amoxiclav and coenzyme Q10 group, the liver sections showed a significant decrease in inflammatory cells, necrosis and degeneration, and regular hepatocytes plates and lobules (Figure 3).

In Coenzyme Q10 group, no remarkable pathological signs were observed in the liver sections (Figure 4).

Table 1) Comparison of the mean±SD concentration of liver biochemical parameters between the studied groups (TSB: Total Serum Bilirubin; ALP: Alkaline Phosphates; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase)

Groups	TSB (mg/dl)	ALP (IU/L)	ALT (IU/L)	AST (IU/L)
Control	0.15±0.03	287.80±35.08	45.60±3.42	133.16±11.13
Amoxiclav	0.18±0.03	470.83±19.80	69.66±3.39	285.16±17.48
Amoxiclav +Q10	0.17±0.02	253.00±22.74	57.33±3.15	97.00±2.36
Coenzyme Q10	0.17±0.03	265.50±25.05	41.30± 3.62	113.20±9.30

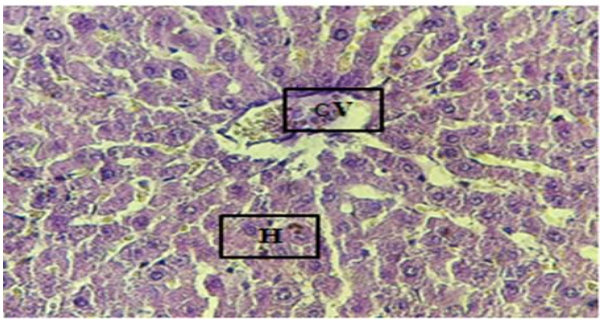

Figure 1) Cross-section of liver in control group
CV: Central Vein, H: Hepatocytes (400X, H&E stain)

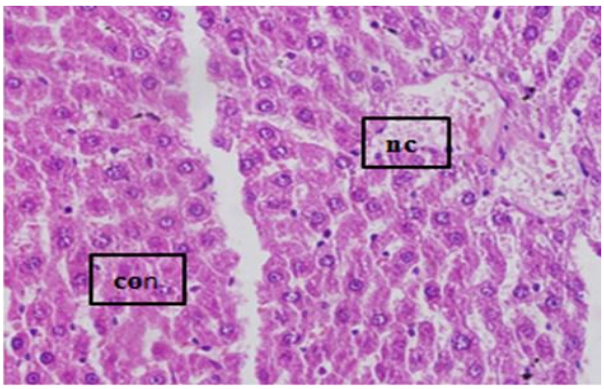

Figure 2) Cross-section of liver in amoxiclav group
nc: necrosis, co: congestion (400X, H&E stain)

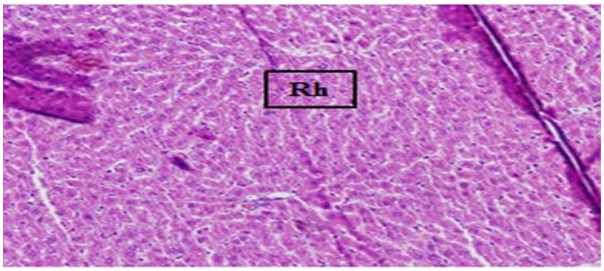

Figure 3) Cross-section of liver in amoxiclav and coenzyme Q10 group
Rh: Regular hepatocytes (400X, H&E stain)

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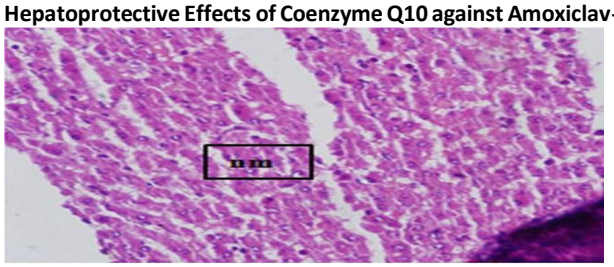

Figure 4) Cross-section of liver in coenzyme Q10 group
nm: no remarkable pathology (400X, H&E stain)

Discussion

The present research was conducted to evaluate the protective, anti-inflammatory, antioxidant, and anti-proliferative role of CoQ10 against hepatotoxic adverse reactions of amoxiclav antibiotic since it is widely prescribed as an antimicrobial agent for the treatment of various infections.

Amoxiclav is generally effective and well tolerated with mild to moderate side effects, but the treatment course could be complicated by an adverse hepatic reaction that could be either dose or duration related or occur unexpectedly as a specific drug reaction [23].

Liver plays the role of detoxifier and excreter of destructive agents against body intoxication. Liver injury occurs following by histopathological changes including degeneration, necrosis, and atrophy of liver parenchymal cells with interstitial connective tissue as well as increasing in liver enzymes, such as AST/ALT, ALP, and plasma total bilirubin level [24].

In the present study, the use of amoxiclav for 30 days led to significant increments in liver enzymes manifested by increased levels of ALT, AST, and ALP as well as TSB, which could be due to either hepatocellular insults or histological destruction [21, 25]. Histological examination revealed hepatic congestion and necrosis together with inflammatory cell infiltration. This finding is in concordance with previous studies in which hepatic injury manifested by hepatic cell damage and cholestasis [26].

Concomitant administration of CoQ10 has significantly decreased the serum level of hepatic enzymes. This is in concordance with other studies [16, 27] in which CoQ10 exhibits potent anti-inflammatory, anti-oxidant, and anti-apoptotic properties even at the gene level. Elshazly *et al*. investigated the ability of CoQ10 to protect against fructose-induced hepatic damage in a rat model and suggested CoQ10 supplement as a possible prophylaxis or treatment candidate for fructose-induced liver injury [16]. Gane *et al*. found that the administration of the mitochondria-targeted anti-oxidant mitoquinone significantly decreased plasma ALT and AST in patients with chronic Hepatitis C Virus (HCV) infection, and this suggests that mitoquinone may decrease necroinflammation in the liver in these patients [27].

In a study, Eftekhari *et al*. demonstrated the protective effects of Coenzyme Q10 Nanoparticles (CoQ10-NPs) on hepatotoxicity induced by Dichlorvos (DDVP) as an organophosphate. They proposed that the CoQ10-NPs have the potential capability to be used as a therapeutic and prophylactic agent for poisoning that is induced by organophosphate agents, especially in the case of DDVP. Furthermore, they stated that CoQ10-NPs are suitable for the treatment of xenobiotic-induced liver diseases [28].

Abed Al-Kareem *et al*. examined the role of the natural and free radical scavenger "CoQ10" against diclofenac-induced hepatic and renal tissue injury in 36 adult Wistar rats. They concluded that diclofenac's toxic effects could be the consequences of mitochondrial dysfunction and free radical effects, and therapeutic supplementation of CoQ10 remarkably diminishes the diclofenac-induced toxic oxidative injury and apoptotic cell death [20].

Histological findings of the liver treated by CoQ10 concomitantly with amoxiclav revealed a clear resolution of inflammation and reduced necrosis with the near restoration of the normal cellular appearance. This is in agreement with other findings that supported the evidence of the protective effect of CoQ10, both at the cellular and molecular levels [27].

Coenzyme Q10 has potent actions in reducing the toxic cellular effects of many compounds by reducing the expression of certain cellular and genetic elements in rat hepatocytes upon hepatotoxicity due to heavy metals exposure [29]. Coenzyme Q10 can be used as an effective therapeutic agent in the treatment and prevention of hepatotoxic adverse drug reactions of many therapeutic agents by reducing oxidative load and the expression of reactive oxygen species by the mitochondria as well as improving mitochondrial functions [30].

Recent data reveal that CoQ10 affects expression of genes involved in human cell signalling, metabolism, and transport and some of the effects of exogenously administered CoQ10 may be due to this property. Coenzyme Q is the only lipid soluble antioxidant synthesized endogenously [31].

In Ashkani Esfahani *et al*.'s study, administration of CoQ10 in TAA-induced liver damage in rat models showed its beneficial effects as a hepatoprotective agent. CoQ10 ingestion also attenuated the neurobehavioral alterations caused by liver dysfunction [32].

In a double-blind, placebo-controlled, randomized clinical trial, Farsi *et al*. evaluated the effects of CoQ10 supplementation on liver enzymes, inflammation status, and adipokines in patients with Nonalcoholic Fatty Liver Disease (NAFLD) and suggested that CoQ10 supplement at a dosage of 100 mg could be effective for improving the systemic inflammation and biochemical variables in NAFLD [33].

According to the results of the present study and previous studies, it seems that the coenzyme Q10 supplement can have a protective effect on liver damage and can be used in the appropriate dose, which the right dose of this supplement for human use should be investigated in future studies.

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Conclusion

Amoxiclav antimicrobial treatment can be complicated by hepatotoxic side effects that could be due to hepatocellular destruction and cholestasis or immunologically mediated. This adverse drug reaction can be effectively minimized by using CoQ10 as a powerful lipid-soluble anti-inflammatory and antioxidant agent that can effectively reduce liver enzymes and restore normal hepatic tissue architecture via its pleiotropic properties.

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Ethical Permission: The study was approved by the ethical committee of the College of Pharmacy, University of Kerbala. Monitoring of the animals in their cages was achieved daily to elucidate the clinical signs.

Conflict of Interests: Nothing has been reported by the authors.

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