
Coenzyme Q10 mitigates Bempedoic Acid-induced hyperuricemia in hyperlipidemic rats

Received: 19/05/2025

Accepted: 29/07/2025

Saya Mohammed Omar¹Nidhal Abdulkader MohammedAli²

ABSTRACT

Background and objective: Hyperlipidemia is a key risk factor for atherosclerotic cardiovascular disease (ASCVD). Bempedoic Acid (BA) is an ATP-citrate lyase inhibitor indicated for statin-intolerant patients, or patients at high risk of ASCVD with hyperlipidemia. However, BA may raise plasma uric acid levels, potentially causing hyperuricemia and gout. Coenzyme Q10 (CoQ10), a natural antioxidant, has anti-inflammatory and renal-protective properties. This study evaluates CoQ10's potential to mitigate BA-induced renal side effects in a hyperlipidemic rat model.

Methods: Forty male Sprague-Dawley rats were divided into five groups: a negative control (normal), a positive control (hyperlipidemic), a BA-treated group (hyperlipidemic rats on BA monotherapy), a BA + CoQ10 group (hyperlipidemic rats receiving BA and CoQ10 combination), and a BA + Allopurinol group (hyperlipidemic rats receiving BA and Allopurinol combination). The positive control and all treatment groups received a high-fat diet to induce and maintain hyperlipidemia throughout the experiment. After 8 weeks of inducing hyperlipidemia, therapeutic interventions were administered for a further 10 weeks. Renal biomarkers (uric acid, serum creatinine, and blood urea nitrogen) and the oxidative stress biomarker malondialdehyde (MDA) were measured.

Results: BA monotherapy significantly raised mean serum uric acid and creatinine compared with the negative control group. Co-administration of CoQ10 significantly lowered both parameters. Mean serum MDA was significantly reduced in all treatment groups compared with the positive control group.

Conclusion: These findings suggest that combining BA with CoQ10 could serve as a therapeutic strategy for hyperlipidemic patients on BA therapy who have compromised renal function.

Keywords: Hyperlipidemia, Hyperuricemia, Bempedoic Acid, Coenzyme Q10, Antioxidant

¹ Department of Pharmacy, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region, Iraq.² Department of Pharmacology, Biophysics and Biochemistry, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region, Iraq.Correspondence: Saya Mohammed Omar, omarmsaya98@gmail.comCopyright © The Author(s) 2026. Open Access. This work is licensed under a [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

INTRODUCTION

Hyperlipidemia refers to elevated blood lipid levels, including cholesterol, low-density lipoproteins (LDL-C), and triglycerides (1). It is a significant risk factor for cardiovascular disease (CVD), including atherosclerotic cardiovascular disease (ASCVD) — a process initiated by endothelial injury from chronic hyperlipidemia, leading to LDL infiltration into arterial walls, oxidative modification, and foam cell formation (1); a regional analysis of patients with acute coronary syndrome in Erbil similarly found hyperlipidemia in two-thirds of cases (2). Management of hyperlipidemia includes both pharmacological and non-pharmacological interventions, such as dietary change and lipid-lowering medication, to reduce CVD risk¹. Bempedoic Acid (BA), first approved in 2020 by the U.S. Food and Drug Administration, is a newer agent indicated for hyperlipidemia treatment in adults with established cardiovascular disease or at high risk of developing CVD (3). BA lowers blood cholesterol by inhibiting the enzyme ATP-citrate lyase (ACL), which is involved in converting citrate to acetyl-CoA₃. By blocking ACL, BA reduces the availability of substrates for 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase — the rate-limiting enzyme in hepatic cholesterol biosynthesis — inhibiting both cholesterol and fatty acid biosynthesis (4). This reduces hepatic very-low-density lipoprotein (VLDL) production and upregulates low-density lipoprotein receptor (LDLR) expression, enhancing LDL-cholesterol (LDL-C) clearance from circulation (3). BA also exhibits anti-inflammatory benefits through stimulation of AMP-activated protein kinase (AMPK) (3). Although BA is generally well tolerated, it is not free from side effects: hyperuricemia has been linked to BA use in clinical studies, which may pose a risk for individuals susceptible to gout or other conditions related to elevated blood uric acid (4). Patients receiving BA

therapy with a previous gout diagnosis or elevated plasma uric acid have been reported to face up to four times the risk of gout (4). Coenzyme Q10 (CoQ10) is an antioxidant synthesized endogenously and is an essential component of the mitochondrial electron transport chain (ETC), critical for adenosine triphosphate (ATP) synthesis by transporting electrons between Complexes I/II and III, and for scavenging free radicals including reactive oxygen species (ROS) when present in its reduced form as ubiquinol; it is known for its antioxidant and anti-inflammatory benefits (5). Preclinical studies have associated CoQ10 administration with reduced oxidative stress biomarkers such as malondialdehyde (MDA) (5), and have shown it preserves glomerular filtration by reducing serum creatinine and uric acid through its ROS-scavenging properties (6). This research therefore aims to evaluate the potential role of CoQ10 in mitigating hyperuricemia induced by Bempedoic Acid (BA) in a hyperlipidemic rat model, by measuring key parameters involved in hyperuricemia, including kidney function (serum creatinine, uric acid, and blood urea nitrogen) and the oxidative stress biomarker MDA.

METHODS

Experimental Animals and Setting

Male Sprague-Dawley rats aged 8-10 weeks and weighing 120-180 g were obtained from, and housed in, the experimental animal house of Hawler Medical University, College of Pharmacy (Erbil, Iraq). Animals were kept in cages (410 x 266 x 185 mm) under hygienic conditions following the National Institutes of Health Guide for the Care and Use of Laboratory Animals (7). Bedding consisted of sawdust, replaced every 5-7 days, and animals were maintained at 22 ± 1°C and 40-60% humidity on a 12-hour light/dark cycle (8). Feeding consisted of standard rat chow (26.02% protein, 66.58%

carbohydrates, 4.35% fat, 27.78% minerals, 0.12% vitamins, 0.08% enzymes) and, for hyperlipidemic groups, a high-fat diet (20% animal fat, 1% cholesterol, 0.5% cholic acid) (8). All groups had ad libitum access to food and water.

Study Design

Forty adult male rats were used in this study. The negative control group (8 rats) received standard rat chow only, with no disease induction or pharmacological intervention throughout the study. Hyperlipidemia was induced in the remaining 32 rats by feeding a high-fat diet (HFD) throughout the study to maintain the hyperlipidemic state (8). The composition and caloric content of the HFD were prepared according to Kelle et al. (8), and administered for eight weeks. Following induction, the 32 rats were randomly divided into four equal groups: positive control, BA-monotherapy, BA + CoQ10, and BA + Allopurinol. The positive control group continued to receive the HFD but no therapeutic intervention. The BA-monotherapy group received Bempedoic Acid following the 8-week induction period. The BA + CoQ10 group received a combination of BA and CoQ10, and the BA + Allopurinol group received a combination of BA and Allopurinol. All hyperlipidemic groups continued to receive the HFD throughout the full 18-week study period.

Drugs and Chemicals

Pure cholesterol and cholic acid powders (Solarbio Science & Technology Co., Ltd., China) were mixed with standard rat chow at 1% and 0.5%, respectively, to induce hyperlipidemia (8). Bempedoic Acid (Nilemdo®) was given by oral gavage at 30 mg/kg body weight (9). Pure Coenzyme Q10 (NuSci, USA) was dissolved in olive oil (Rafael Salgado, Spain) and given at 10 mg/kg by oral gavage (10). Allopurinol tablets

(Accord Healthcare, UK) were administered orally at 5 mg/kg (11).

Ethics Committee Approval

The study was approved by the Ethics Committee at the College of Medicine, Hawler Medical University, following the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985) (7).

Blood Sampling

All rats were anesthetized by intraperitoneal injection of xylazine (Xylanit®, 0.2 mg/kg) and ketamine (Alfasan®, 0.8 mg/kg), following Kumar and Clover (12), and sacrificed by cervical dislocation at the end of the experiment¹². Blood samples were drawn by cardiac puncture and centrifuged at 4000 rpm for 10 minutes to separate serum for analysis (13).

Biochemical Parameters

Rat serum was used to measure the renal biomarkers uric acid (UA), serum creatinine (SCr), and blood urea nitrogen (BUN) by spectrophotometric assay, and malondialdehyde (MDA) by enzyme-linked immunosorbent assay (ELISA) using a rat kit (SunLong Biotech Co. Ltd., China).

Statistical Analysis

Data were analyzed using SPSS-30 software, with quantitative data presented as mean ± standard error of the mean (SEM). The Shapiro-Wilk test was used to assess normality, and differences between groups were analyzed by one-way analysis of variance (ANOVA). Differences were considered significant at $p \leq 0.05$.

RESULTS

Effect of Bempedoic Acid (30 mg/kg) and Its Combination with Coenzyme Q10 (10 mg/kg) or Allopurinol (5 mg/kg) on Renal Function Biomarkers in Hyperlipidemic Rats

As shown in Table 1, the mean serum UA level of the negative control group (1.013 ± 0.09 mg/dl) did not differ significantly ($p > 0.05$) from that of the positive control group (1.08 ± 0.16 mg/dl). BA administration (30 mg/kg/day, 10 weeks) significantly increased the mean serum UA level to 2.05 ± 0.15 mg/dl, significantly higher ($p < 0.05$) than in all other groups. In the groups co-administered CoQ10 or Allopurinol with BA, mean serum UA levels (1.14 ± 0.09 mg/dl and 1.28 ± 0.05 mg/dl, respectively) did not differ

significantly ($p > 0.05$) from the negative control group. The mean SCr level of the positive control group (0.36 ± 0.02 mg/dl) was not significantly different ($p > 0.05$) from the negative control group (0.33 ± 0.04 mg/dl). In the BA-treated group, the mean SCr level (0.43 ± 0.03 mg/dl) was significantly higher ($p < 0.05$) than the negative control group, though not significantly different from the positive control group. Groups receiving BA + CoQ10 or BA + Allopurinol had mean SCr levels of 0.34 ± 0.02 mg/dl and 0.38 ± 0.01 mg/dl, respectively, both statistically non-significant ($p > 0.05$) compared with the positive control group (Table 1). Mean BUN levels showed non-significant ($p > 0.05$) differences across the positive control and all intervention groups, as shown in Figure 1.

Table 1. Effect of Bempedoic Acid (30 mg/kg) alone and in combination with CoQ10 or Allopurinol on kidney function biomarkers in hyperlipidemic rats

Biomarker	NC	PC	BA	BA+CoQ10	BA+Allo
UA $\pm$ SEM (mg/dl)	1.013 ± 0.09 abde	1.08 ± 0.16 bade	2.05 ± 0.15 c	1.14 ± 0.09 dabe	1.28 ± 0.05 eabd
SCr $\pm$ SEM (mg/dl)	0.33 ± 0.04 abde	0.36 ± 0.02 bacde	0.43 ± 0.03 cbde	0.34 ± 0.02 dabce	0.38 ± 0.01 eabcd

NC = negative control; PC = positive control; BA = Bempedoic Acid; Allo = Allopurinol. Different superscript letters within a row indicate a significant difference ($p < 0.05$); shared letters indicate no significant difference ($p > 0.05$).

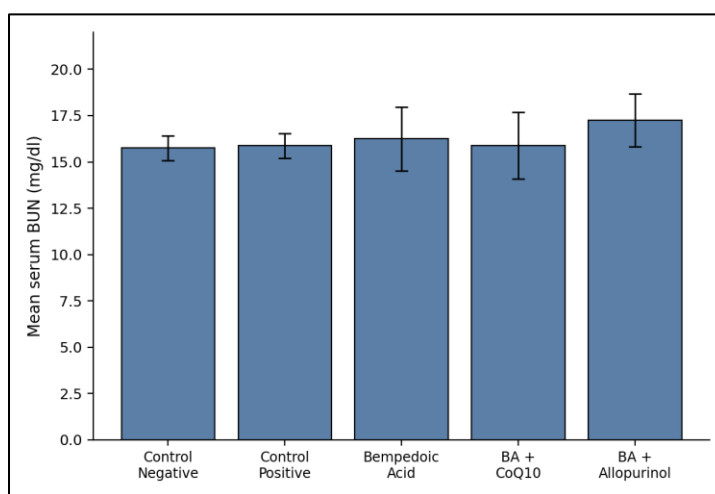


Figure 1. Effect of Bempedoic Acid (30 mg/kg) and its combination with Coenzyme Q10 (10 mg/kg) or Allopurinol (5 mg/kg) on blood urea nitrogen level in hyperlipidemic rats

Effect of Bempedoic Acid (30 mg/kg) and Its Combination with Coenzyme Q10 (10 mg/kg) or Allopurinol (5 mg/kg) on Mean Serum Malondialdehyde Levels in Hyperlipidemic Rats

The positive control group showed a significantly ($p < 0.001$) elevated mean serum MDA level (46.48 ± 1.42 ng/ml) compared with the negative control group (28.62 ± 1.68 ng/ml). BA monotherapy substantially reduced mean serum MDA levels

(28.57 ± 2.09 ng/ml), a significant reduction ($p < 0.001$) compared with the positive control group, and not significantly different ($p > 0.05$) from the negative control group. Both combination therapies significantly reduced mean serum MDA levels compared with the positive control group: BA + CoQ10 (33.84 ± 2.69 ng/ml, $p = 0.01$) and BA + Allopurinol (36.05 ± 3.11 ng/ml, $p = 0.03$), as shown in Table 2.

Table 2. Effect of Bempedoic Acid (30 mg/kg) and its combination with Coenzyme Q10 (10 mg/kg) or Allopurinol (5 mg/kg) on mean serum malondialdehyde levels in hyperlipidemic rats

Group (n=8)	MDA, Mean $\pm$ SEM (ng/ml)	P vs PC
Negative control	28.62 $\pm$ 1.68 b	<0.001
Positive control	46.48 $\pm$ 1.42 a	—
Bempedoic Acid	28.57 $\pm$ 2.09 b	<0.001
BA + CoQ10	33.84 $\pm$ 2.69 b	0.01
BA + Allopurinol	36.05 $\pm$ 3.11 b	0.03

a: significantly different ($p < 0.05$) vs negative control (NC). b: significantly different ($p < 0.05$) vs positive control (PC).

DISCUSSION

BA administration has been associated with elevated mean serum uric acid, potentially predisposing patients to hyperuricemia and gout (3). This study investigated the therapeutic potential of CoQ10 in alleviating BA-induced renal side effects in a hyperlipidemic rat model.

BA monotherapy (30 mg/kg/day) for 10 weeks induced a significant ($p < 0.05$) increase in mean serum uric acid compared with the negative control, positive control, and all intervention groups. This elevation is expected, as studies have linked BA treatment with rising UA levels from as early as week 4, along with gout incidence among BA-treated patients (14). The major metabolite of BA has been shown to compete with organic anion transporter 2 (OAT2) in the liver and renal proximal tubules, impairing uric acid excretion (15), which

explains the significantly ($p < 0.05$) higher mean serum uric acid observed following BA administration in this study. Such an effect necessitates monitoring uric acid levels, especially in people with gout (16). Similar to the current results, clinical trials have also demonstrated significant increases in serum uric acid following BA treatment, resulting in gout in 1-2% of patients (14, 17).

To mitigate the increased uric acid levels, we used CoQ10 as an adjunct to BA. CoQ10 is produced endogenously and has anti-inflammatory and antioxidative effects previously associated with reno-protective benefits (18).

BA and CoQ10 combination produced non-significant ($p > 0.05$) differences compared with the negative control, while co-administration of CoQ10 with BA produced a significant ($p < 0.05$) reduction

in mean serum UA compared with the BA-monotherapy group, indicating a reversal of the elevated UA levels seen following BA monotherapy. This indicates that CoQ10 exhibits uric acid-lowering benefits when used in combination with BA. A significant reduction of serum uric acid by CoQ10 in hyperuricemia patients has recently been illustrated by Kuang et al. (19) CoQ10 has shown promise in mitigating renal oxidative stress and inflammation, and may exert protective effects by reducing ROS generation and, subsequently, uric acid production, through inhibition of xanthine oxidase (XO) activity — a key enzyme in the formation of uric acid from hypoxanthine (5).

For further comparison, Allopurinol — a known urate-lowering therapy (ULT) that acts by inhibiting xanthine oxidase — was investigated (11). The BA + Allopurinol group served as a standard against which to compare the uric acid-lowering effects of CoQ10.

The BA + Allopurinol group showed a significant ($p < 0.05$) reduction in mean serum uric acid compared with the BA-monotherapy group, and a non-significant ($p > 0.05$) change compared with the negative control group. This reveals that Allopurinol, through its mechanism of action and proposed antioxidant effects, ameliorated the significant BA-induced increase in mean serum UA (21).

An elevated mean SCr level was also observed with BA monotherapy in this study: 0.43 ± 0.03 vs. 0.33 ± 0.04 mg/dl in the negative control group, a significant difference ($p < 0.05$). Creatinine is an endogenous substance produced by skeletal muscle catabolism. It is primarily filtered at the glomerulus and is additionally secreted by various organic anion and cation transporter proteins in the proximal tubular cells (22), and the significantly ($p = 0.042$) higher mean serum creatinine found in this study

following BA monotherapy is related to competitive interaction between the major BA metabolites — glucuronides of bempedoic acid and bempedoyl-CoA — and OAT2, which results in elevated serum creatinine following BA administration (15, 23). Increases in mean serum creatinine and uric acid following BA monotherapy in the current study have also been reported previously, attributed to BA's competition for OAT2, which stresses the importance of monitoring UA and SCr levels during BA therapy (16, 24).

In the current study, co-treatment of BA with CoQ10 reduced the BA-induced elevation in mean serum SCr, although this was not statistically significant ($p > 0.05$). The molecular mechanism behind CoQ10's reduction of SCr has been attributed to downregulation of proinflammatory signaling pathways, including nuclear factor- κ B (NF- κ B) and inducible nitric oxide synthase (iNOS), and to its role in preserving antioxidants such as glutathione, which neutralize reactive oxygen species (ROS) (18, 25). In alignment with the current findings, reduced SCr levels with CoQ10 have previously been reported by Couto et al. (25).

Similar results were observed with Allopurinol co-administration: SCr levels were reduced compared with BA monotherapy, though not statistically significantly ($p > 0.05$), and the reduction was less pronounced than with CoQ10 co-administration. Similar to the current study, a review by Stamp et al. (26) included studies that observed non-significant reductions in serum creatinine after 12 months of Allopurinol treatment in patients with renal disease. Although Allopurinol inhibits xanthine oxidase and lowers uric acid — potentially reducing renal inflammation and oxidative stress and improving overall renal function — it did not significantly affect serum creatinine levels in that review. A systematic review and meta-analysis by

Sharbaf et al. (27) similarly reported statistically non-significant reductions in serum creatinine with Allopurinol treatment in chronic kidney disease (CKD) patients, and instead focused on estimated glomerular filtration rate (eGFR) as the primary outcome for improved kidney function.

There was a statistically non-significant ($p > 0.05$) difference across all groups for BUN levels. Although elevated BUN levels have been reported with BA treatment in previous studies (14, 16), in the current study the BA-monotherapy group showed non-significant ($p > 0.05$) changes in mean serum BUN compared with the positive control group. Other studies used larger study populations, whereas the current study used a limited number of hyperlipidemic rats, which may explain the non-significant results observed for BUN (16, 28). The increases in serum creatinine and BUN observed in other studies have been attributed to OAT2 inhibition in the renal tubules (28). Studies have highlighted the reno-protective effects of CoQ10 in animal models of kidney injury (6, 18). A study by Kara (20) showed the reno-protective effects of CoQ10 when administered to rats with cyclophosphamide-induced kidney damage. The mechanism behind CoQ10's protection of kidney function is proposed to relate to its antioxidant effects — acting as an electron carrier in mitochondrial Complex I/II and scavenging superoxide radicals (O_2^-) (18).

Malondialdehyde (MDA) is a well-established biomarker of lipid peroxidation and oxidative stress, commonly elevated in models of hyperlipidemia and associated renal or cardiovascular pathologies (29), with oxidative stress biomarkers similarly studied across various local patient populations in the Kurdistan region (30). In the present study, the significant ($p < 0.001$) increase in mean serum MDA in the positive control group

compared with the negative control group indicates that the hyperlipidemic state induced oxidative stress, raising mean serum MDA in this group. Numerous studies have found that serum MDA is higher in individuals with hyperlipidemia and decreases with antioxidant supplementation, with similar observations reported in animal models of hyperlipidemia (31, 32). Hyperlipidemia is known to be associated with increased production of lipid peroxidation products, which heightens oxidative stress and increases ROS production in hyperlipidemic subjects (32). Eventually, oxidative stress leads to an imbalance between prooxidant and antioxidant mechanisms and facilitates the escape of free radicals from the mitochondrial electron transport chain (32). MDA, one of the lipid peroxidation byproducts, is produced when free radicals attack membrane lipoproteins and polyunsaturated fatty acids (29). Consequently, the oxidative stress driven by progressive hyperlipidemia contributes to increased serum MDA levels. This is the most plausible explanation for the significantly higher mean serum MDA found in the positive control group compared with the negative control group in the present study, as the high-fat diet was maintained throughout the entire experimental period in the positive control group.

Treatment with BA monotherapy led to a significant ($p < 0.001$) reduction in mean serum MDA compared with the positive control group. Bempedoic acid has been shown to activate the 5' adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, known to attenuate oxidative stress and inhibit ROS production (33). The reduction in mean serum MDA to levels comparable with the negative control group underscores BA's therapeutic promise in managing oxidative stress. This antioxidant effect is consistent with recent findings by Mosaad, El-Sayed and Morsy (33), who demonstrated that BA reduced MDA levels in

tamoxifen-induced steatohepatitis in rats by approximately 55%, attributed to AMPK activation. The group receiving BA in combination with CoQ10 showed a significant ($p < 0.001$ vs. positive control) reduction in mean serum MDA. CoQ10 is known for its role in mitochondrial bioenergetics and as a lipid-soluble antioxidant. Dłudla et al. (34) conducted a meta-analysis including numerous clinical trials and preclinical models, confirming that CoQ10 supplementation significantly reduces MDA levels, reflecting its potent anti-lipid-peroxidation effect. Moreover, in a study by Malik et al. (35), rats pretreated with CoQ10 exhibited significantly lower MDA levels and histologically improved renal architecture, demonstrating CoQ10's nephroprotective effects against oxidative damage.

The BA + Allopurinol group also showed a significant ($p = 0.03$ vs. positive control) reduction in MDA levels. Allopurinol, as a xanthine oxidase inhibitor, reduces uric acid production and attenuates ROS generated via xanthine metabolism (29, 36). This reduction can be explained by the alleviation of oxidative stress through xanthine oxidase inhibition (36). The antioxidant properties of BA, alone or combined with CoQ10 or Allopurinol, explain the significantly ($p = 0.01$ and $p = 0.03$) lower mean serum MDA in the treatment groups compared with the positive control group, and further explain the non-significant ($p > 0.05$) differences between any treatment group and the negative control group.

CONCLUSION

Co-administration of BA with Coenzyme Q10 (CoQ10) significantly reduced the BA-induced elevation in mean serum uric acid and creatinine, mitigating BA-induced hyperuricemia and adverse renal effects. BA monotherapy and its combinations with CoQ10 or Allopurinol exhibited antioxidant activity by significantly alleviating the

hyperlipidemia-induced increase in the oxidative stress biomarker MDA. These findings support CoQ10 as a promising adjunct therapy to mitigate BA's renal side effects.

COMPETING INTEREST

The authors declare that they have no competing interests.

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