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Hepatoprotective effect of N-acetylcysteine against augmentin-induced biochemical alterations of liver function in rats

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Abstract

Background: Augmentin is a common antibiotic that can cause liver injury. It increases oxidative stress and damages liver cells. N-acetylcysteine (NAC) is known for its antioxidant and protective effects on the liver. This study aimed to evaluate the protective role of NAC against augmentin-induced liver damage in rats by measuring biochemical markers, oxidative stress indices, lipid profile, and histopathology. **Methodology:** Forty male rats were divided into four groups (10 each). Control group received basal diet. T1 received augmentin (30 mg/kg/day). T2 received NAC (150 mg/kg/day). T3 received NAC plus augmentin at the same doses. Oral treatments lasted for 5 weeks. Blood samples were collected for biochemical tests (liver function enzymes and lipid profile). **Results:** The animals of T1 group showed a significant ($p < 0.05$) rise of liver enzymes, and lipid profile parameters, and a decrease in HDL, total protein and albumin as compared with the control. While T2 depicted a significant correction of these alterations toward the control values ($p < 0.05$). T3 explained a significant improvement in liver enzymes, lipid profile, and bilirubin, approaching control levels ($p < 0.05$). **Conclusions:** NAC effectively reduced augmentin-induced biochemical and histological liver damage. It has antioxidant, anti-inflammatory, and lipid-stabilizing effects. NAC may be considered as a supportive therapy in drug-induced hepatotoxicity.

Keywords: Augmentin, hepatotoxicity, liver, N-acetylcysteine

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Introduction

Augmentin, a combination of amoxicillin and clavulanic acid, is widely prescribed for bacterial infections. However, its use is often linked with drug-induced liver injury (Appiah *et al*., 2023). The liver is the primary site for drug metabolism and is highly susceptible to oxidative stress caused by reactive oxygen species (ROS). Increased liver enzymes such as ALT, AST, ALP, and GGT indicate hepatocellular damage after augmentin exposure (Ali *et al*., 2018). High bilirubin means the liver cannot clear waste well. It is also a sign of cholestasis (Teschke *et al*., 2021). Augmentin is known to harm the liver. It disrupts mitochondria and triggers immune responses (Delemos *et al*., 2016; Appiah *et al*., 2023). Because of this, many studies looked for protective agents that can prevent drug-induced liver damage.

N-acetylcysteine (NAC) is a sulfur compound with strong antioxidant effects. It restores glutathione inside cells and clears free radicals. This lowers oxidative stress and limits tissue injury (Aldini *et al*., 2018). Experiments and clinical studies show that NAC reduces enzyme leakage and improves hepatocyte survival (Nikbaf-Shandiz *et al*., 2023; Sukumaran *et al*., 2023). NAC also regulates inflammation by lowering TNF-α and NF-κB activity (Albeltagy *et al*., 2021). Another research shows that it protects mitochondria, balances redox state, and prevents apoptosis (Ameri *et al*., 2024). These combined effects make NAC a promising option against augmentin-induced hepatotoxicity. Augmentin also affects lipid metabolism. In animals it raises cholesterol, triglycerides, LDL, and VLDL, and lowers HDL (Ding *et al*., 2024). These shifts raise cardiovascular risk. NAC improves lipid levels by reducing lipid peroxidation and supporting nitric oxide–mediated vascular health (Mahmoudinezhad *et al*., 2023; Haryanti *et al*., 2025). Another work shows that NAC decreases oxidized LDL and foam cell formation, lowering atherosclerosis risk (Shagari *et al*., 2025). By restoring lipid balance, NAC supports both liver and heart health. Histology confirms these biochemical changes. Augmentin causes necrosis of hepatocytes, sinusoidal congestion, bile duct damage, and inflammatory infiltration (Ayala *et al*., 2014; El-Kholy *et al*., 2019; Ribeiro, 2023). NAC improves the liver tissue by reducing necrosis, swelling, and inflammation, keeping the structure close to normal Galicia-Moreno *et al*., 2024). Together, these results confirm that NAC protects the liver against augmentin toxicity at both biochemical and structural levels. This study aimed to evaluate the protective role of NAC against augmentin-induced liver damage in rats by measuring biochemical markers, oxidative stress indices, lipid profile, and histopathology.

Materials and Methods

Animals and experimental design

Forty healthy male rats weighing 300–350 g were placed in the animal house of the College of Veterinary Medicine, University of Baghdad. The room was maintained at 20–25°C with a 12 h light/dark cycle. Rats were acclimated for 10 days before starting the trial. Food and water were given ad libitum. The rats were randomly divided into four equal groups (10 rats each). The control group received water and standard pellet diet. Group T1 was treated orally with augmentin at 30 mg/kg/day. Group T2 received NAC orally at 150 mg/kg/day. Group T3 received both NAC 150 mg/kg/day and augmentin 30 mg/kg/day. Treatments lasted for 5 weeks. This design allowed comparison between the protective effects of NAC alone and combined with Augmentin. The treatments were given daily using oral gavage. The doses were selected based on an earlier report of augmentin-induced hepatotoxicity and NAC hepatoprotection (Ahmed *et al*., 2020). The animals were closely monitored for behavior, feeding activity, and signs of stress during the experimental period. At the end of the 5 weeks, all rats were fasted overnight before samples collection.

Ethical approval

Ethical approval was obtained from the institutional committee for animal care (P.G. 2476 on 30/12/2024) at the College of Veterinary Medicine, University of Baghdad. The study was conducted according to laboratory animal handling guidelines.

Blood and tissue samples collection

On the 35th day, the rats were anesthetized, and blood was collected directly from the heart. The blood was placed in gel tubes and centrifuged at 1,500 × g for 10 minutes at 4°C. The serum was separated and stored at -20°C until biochemical analysis. The samples were thawed only once to avoid degradation. The serum was used to measure liver enzymes, lipid profile, oxidative stress markers, and inflammatory cytokines.

Biochemical analysis

Serum ALT, AST, and ALP were measured using GIESSE diagnostic kits (ELabScience, China). The enzyme activity was determined kinetically. The GGT activity was estimated using a SIMT kit (ElabScience, China). Serum albumin and bilirubin were quantified using ELISA kits (ElabScience, China). The absorbance was read with a microplate reader following kit protocols. Total cholesterol, triglycerides, LDL, HDL, and VLDL were estimated enzymatically using commercial kits (Linear Chemicals, Spain).

Statistical analysis

Data were analyzed using SPSS (version 2019). Values were expressed as a mean± standard error (SE). One-way ANOVA was used to test differences among groups. Least Significant Difference (LSD) was applied for post-hoc comparison. A P value <0.05 was considered statistically significant.

Results

Liver function enzymes (ALT, AST, ALP)

Rats treated with augmentin (T1) showed a significant ($p<0.05$) rise in serum ALT, AST, and ALP compared with the control (Table 1). In contrast, NAC groups (T2 and T3) showed enzyme activity values close to the control group (Table 1).

Table 1: Effects of the oral administration of augmentin, NAC and both on serum ALT, AST, and ALP levels in male rats (U/L).

Group	Liver enzymes(U/L)		
	ALT	AST	ALP
Control	0.47±27.81B	1.06±26.52B	1.43±39.46B
T1	1.10±40.01A	1.55±32.52A	6.28±58.17A
T2	0.73±28.29B	0.94±27.13B	2.46±40.95B
T3	0.22±28.83B	0.97±26.37B	2.48±41.35B
LSD	2.141 *	3.485 *	10.994 *

Means having with the different letters in same column differed significantly, * (P≤0.05). C: control group, T1 group: 30 mg/kg BW of augmentin, T2 group: 150 mg/kg BW of NAC, T3 group: 150 mg/kg BW of NAC and 30mg/kg BW of augmentin

Serum proteins

Total protein levels showed a significant decline in T1 rats compared with the control. NAC groups showed higher values in T2 and T3. However, the increase in T2 and T3 was not statistically significant compared to the control (P>0.05) (Figure 1).

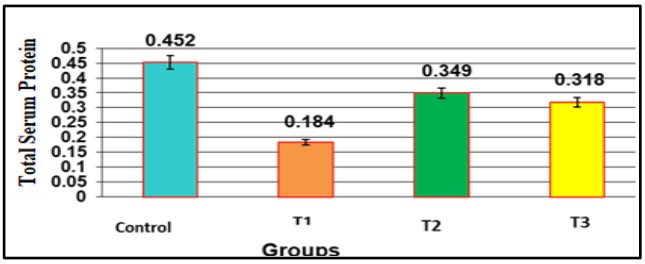

Figure 1: Effect of oral administration of NAC and augmentin on Total Serum Protein (g/dl) in male rats. LSD=0.214. C: Control group, T1 group: 30mg/kg BW of augmentin, T2 group: 150 mg/kg BW of NAC, T3 group: 150 mg/kg BW of NAC and 30mg/kg BW of augmentin

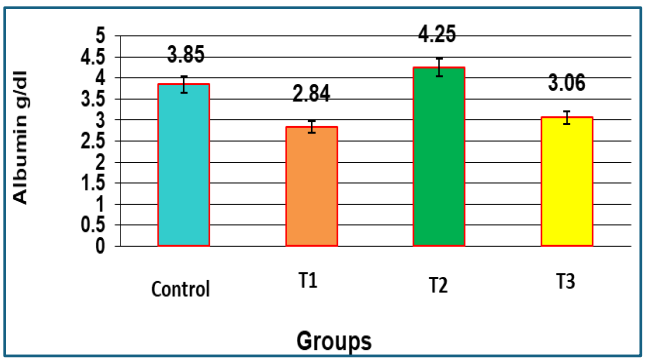

Figure 2: Effect of oral administration of NAC and augmentin on Serum Albumin (g/dl) in male rats. LSD=0.995. C: Control group, T1 group: 30 mg/kg BW of augmentin, T2 group: 150 mg/kg BW of NAC, T3 group: 150 mg/kg BW of NAC and 30 mg/kg BW of augmentin

Serum albumin levels also declined significantly in T1 rats compared to the control. In contrast, NAC-treated rats, especially the T2 group, had higher albumin levels compared with the control (Figure 2).

Lipid profile

Compared to the control group, individuals on augmentin alone (T1) were noted to have statistically a significant increase in total cholesterol, triglycerides, LDL, and VLDL, and an increase in the VLDL fraction. Furthermore, augmentin alone (T1), was observed to lead to a decrease in HDL levels. NAC alone (T2), along with NAC and augmentin (T3) were able to keep total cholesterol, triglycerides, LDL, and VLDL levels within control levels and were also able to maintain HDL levels at control levels. The differences observed and stated above were statistically validated with the LSD test for Chol, TG, HDL, LDL, and VLDL. Taken together, T1 resulted in the presence of hyperlipidemia, while T2 and T3 avoided the presence of dyslipidemia and preserved HDL, as shown in Table 2.

Table 2: Effects of the oral administration of augmentin, NAC and both on serum Lipid profile in male rats (mg/dl)

Group	lipid profile(mg/dl)				
	Cholesterol	Triglyceride	HDL	LDL	VLDL
Control	4.69±180.72B	2.68±175.57B	1.70±39.87A	5.60±105.82B	0.53±35.11B
T1	18.32±230.52A	7.08±256.34A	0.51±23.65B	18.32±150.20A	1,41±51.26A
T2	8.87±179,14B	0.92±174.52B	0.76±39.11A	8.51±103.61B	0.2335.62B
T3	9.21±180.26B	2.56±174.12B	1.48±38.29A	3.71±109.24B	0.6534.32B
LSD	34,234 *	12.061 *	3.660 *	31.539 *	2.495 *

Means having with the different letters in same column differed significantly, * (P≤0.05). C: Control group, T1 group: 30 mg/kg BW of augmentin, T2 group: 150 mg/kg BW of NAC, T3 group: 150 mg/kg BW of NAC and 30 mg/kg BW of augmentin

Estimation of total bilirubin

Total bilirubin levels in T1 were significantly higher in comparison to the control group (P≤0.05). Conversely, T2 and T3 (NAC administered alone or with augmentin) both reduced bilirubin levels to that of the control group, there being no significant difference between the control group and T2 or T3. This suggests that NAC has a possible protective role (Figure 3).

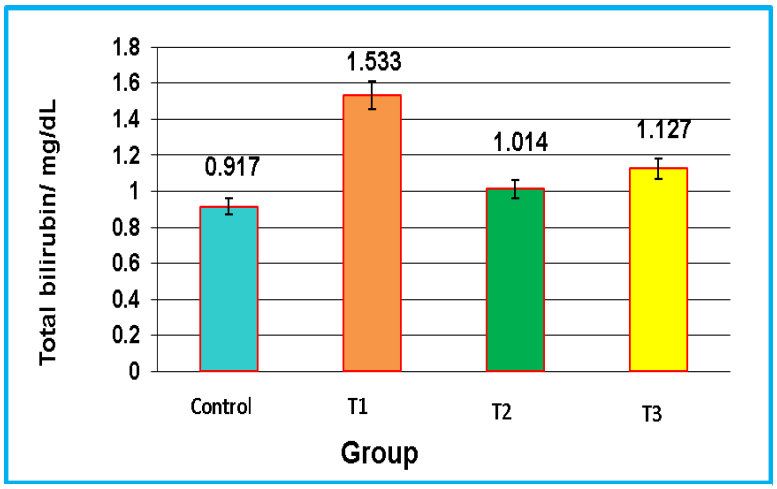

Figure ٣: Effect of oral administration of NAC and augmentin on total bilirubin (mg/dl) in male rats. LSD=0.163. C: Control group, T1 group: 30 mg/kg BW of augmentin, T2 group: 150 mg/kg BW of NAC, T3 group: 150 mg/kg BW of NAC and 30 mg/kg BW of augmentin. LSD=0.425

Estimation of gamma-glutamyl transferase (GGT)

GGT increased in T1, which was significantly higher than other groups ($P < 0.05$). T2 and T3 were near the control (Figure 4) with an LSD of 0.851.

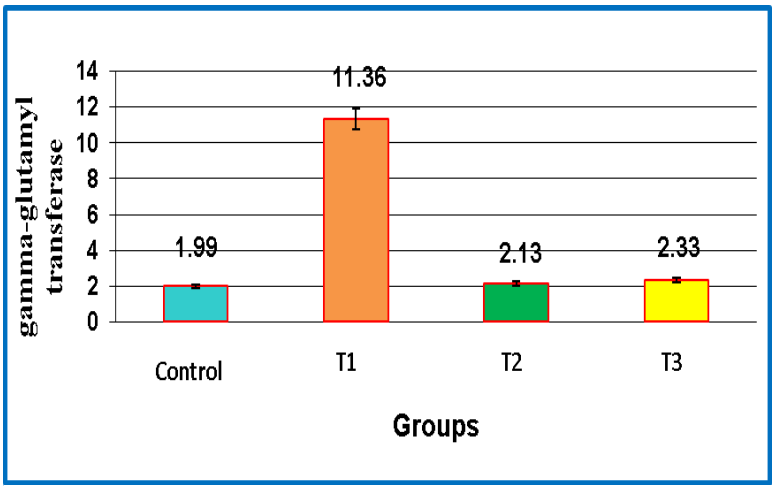

Figure ٤: Effect of oral administration of NAC and augmentin on GGT (U/L) in male rats. LSD=0.851. C: Control group, T1 group: 30 mg/kg BW of augmentin, T2 group: 150 mg/kg BW of NAC, T3 group: 150 mg/kg BW of NAC and 30 mg/kg b.w of augmentin

Discussion

Rats treated with augmentin experienced a statistically significant increase in direct bilirubin ($P \leq 0.05$) with cholestatic involvement, coupled with a mixed injury enzyme pattern (elevated ALP/GGT with ALT/AST and AST). This constellation indicates impaired canalicular bile transport and concurrent hepatocellular damage, a profile characteristic of amoxicillin–clavulanate–associated liver injury. Augmentin (amoxicillin-clavulanate) triggers an idiosyncratic liver injury as a consequence of immune system mediated damage to hepatocytes and cholestasis. Drug–protein adducts form and provoke inflammation, induce a hyperoxic state, and trigger oxidative stress. Interference of bile-acid transport results in injury to the canalicular membranes of hepatocytes. Augmentin

causes hepatocyte injury as evidenced by cytosolic leakage of ALT/AST, damage to the canalicular/biliary pole as evidenced by an increase in ALP/GGT, and impaired excretion of bilirubin as evidenced by an elevated total bilirubin level (Delemos *et al*., 2016).

The findings of the current study match the reports of Teschke *et al*. (2021), who showed that antibiotics and herbs can cause hepatotoxicity with clear biochemical alterations. Delemos et al. (2016) also described similar increases in bilirubin and enzymes in patients with augmentin-induced injury. Mulu and Birhanu (2024) reported prolonged cholestatic liver damage in a clinical case, highlighting the similarity between experimental models and human findings. Moreno-Torres *et al*. (2024) further explained that drug-induced cholestasis often shows raised bilirubin and bile duct damage. On the contrary, NAC (alone or with Augmentin) kept bilirubin and enzyme levels close to control values, suggesting a protective effect against cholestatic and hepatocellular components in this model.
Augmentin caused an increase hepatocellular pattern of injury: ALT and AST increased significantly compared to control ($P \leq 0.05$) while the changes in ALP/GGT were relatively minor. By conventional criteria (R-value using ALT/ALP relative to ULN), this profile is consistent with damage to primary hepatocytes and not isolated cholestasis. The concurrent increase in direct bilirubin implies some cholestatic component, however, the pattern of the enzymes is predominantly of hepatocellular injury.

Elevated ALT and AST reflect leakage of enzymes from damaged hepatocytes, while increased ALP suggests biliary obstruction. NAC treatment alone or combined with augmentin preserved enzyme levels near baseline, showing strong hepatoprotection. These findings confirm that NAC prevented hepatocyte damage and preserved liver integrity. Markers of oxidative stress also supported the role of free radicals in augmentin toxicity. As Zhuang *et al*. (2022) noted for other antibiotics, Augmentin seems to start mitochondrial dysfunction and oxidative stress by impairing electron transport, increasing reactive oxygen species, and opening the mitochondrial permeability transition pore. This promotes lipid peroxidation (↑MDA) and depletion of GSH, which triggers inflammatory NF-κB/TNF-α signaling, destabilizes hepatocyte membranes, and causes the ALT/AST leakage we saw—the hepatocellular pattern. Simultaneously, Timor-López *et al*. (2025) linked the oxidative stress and cholestasis we described to the disruption of canalicular transporters (BSEP/ABCB11, MRP2) and tight junctions. These actions promote the reduction of bile flow, increase direct bilirubin, and cause ALP and GGT to change with cholestasis. The oxidative stress also fails to regulate the FXR–SHP–CYP7A1 axis of bile-acid synthesis and the PPARα/SREBP-1c signaling pathways on lipids. This is the likely reason for the increase in total cholesterol, triglycerides, LDL, and VLDL and the decrease in HDL in T1. The increase of bilirubin, ALT/AST/ALP/GGT, and the cholesterol profile in T2 and T3 suggest NAC treatment which, along with stabilizing the mitochondria, and providing cysteine for GSH synthesis and ROS scavenging, preserved bile salt transport.

Sukumaran *et al*. (2023) confirmed that NAC reduced oxidative stress in patients with anti-tuberculosis drug injury. Zavala-Valencia *et al*. (2024) reported that NAC protected against cisplatin toxicity by replenishing antioxidant defenses, while Galicia-Moreno *et al*. (2024) highlighted its potential in restoring liver redox homeostasis and modulating epigenetic pathways. These studies and those of the current investigation confirm that NAC is effective in restoring antioxidant capacity and reducing oxidative burden.

No inflammatory parameters were used. Lee *et al*. (2004) reported that serum GGT is a sign of oxidative and inflammatory stress. This explains its rise in the augmentin group. Chiang and Ferrell (2020) noted that changes in bile acid pathways during stress can worsen liver inflammation Stress disrupts bile-acid homeostasis by suppressing FXR–FGF19 signaling and impairing canalicular exporters (BSEP/ABCB11, MRP2), causing intrahepatic bile-acid accumulation and cholestasis. Hydrophobic bile acids then damage hepatocyte membranes, trigger JNK, generate ROS, and induce mitochondrial/ER stress, leading to ALT/AST leakage. In parallel, they activate innate-immune pathways (NLRP3 inflammasome, NF-κB/TLR4) and, with gut–liver crosstalk (LPS translocation), amplify cytokine production. The net effect is worsened hepatic inflammation with elevated ALP/GGT and direct bilirubin alongside hepatocellular injury. Liu *et al*. (2019) showed that NAC protects cells by controlling antioxidant enzymes. Ding *et al*. (2024) found that NAC reduced oxidative stress in hyperlipidemia. Mahmoudinezhad *et al*. (2023) reported that NAC improved endothelial function, showing its systemic effect.

Lipid profile changes in augmentin-treated rats were corrected by NAC. Haryanti *et al*. (2025) found that NAC reduced oxidized LDL and foam cell formation in atherosclerosis. Appiah *et al*. (2023) reported that augmentin alters lipid metabolism in humans and raises metabolic risks. The pathways described above account for the increases in Augmentin associated lipid metabolism impairment of TG, TC, and LDL/VLDL and the depression of HDL. Augmentin-induced hepatotoxicity in our model was accompanied by dyslipidemia and classical histopathology (necrosis, sinusoidal congestion, and inflammatory infiltrates), consistent with prior descriptions in rats (El-Kholy *et al*., 2019; Appiah *et al*., 2023). Mechanistically, oxidative stress perturbs lipid pathways—upregulating lipogenesis and impairing β-oxidation thereby worsening triglyceride and LDL/VLDL elevations (Ali *et al*., 2018). Antioxidant interventions counter these changes: plant-derived antioxidants such as cinnamon extract improved lipid balance and attenuated injury in augmentin models (El-Kholy *et al*., 2019), while N-acetylcysteine (NAC) stabilized mitochondria, replenished glutathione, and limited lipid peroxidation (Ameri *et al*., 2024). In our experiment, NAC alone or combined with augmentin maintained near-normal liver architecture and corrected the biochemical profile, aligning with reports of preserved histology and reduced inflammatory/oxidative stress under NAC or antioxidant regimens (Sukumaran *et al*., 2023; Galicia-Moreno *et al*., 2024). Collectively, these converging data indicate that NAC provides meaningful hepatoprotection in augmentin injury by restoring redox balance, normalizing lipid metabolism, and preserving hepatocellular integrity.

Conclusions

N-acetylcysteine (NAC) with amoxicillin–clavulanate hepatotoxicity of a primarily hepatocellular pattern with cholestasis was able to lower hepatic enzymes (ALT/AST and ALP/GGT) and direct bilirubin and dyslipidemia. Alignment of protection with restoration of redox homeostasis (decrease MDA, increase GSH), mitochondrial stabilization, and decreased inflammatory signaling, with canalicular bile-salt (e.g., BSEP/MRP2) and histoarchitecture preservation. NAC rebalanced bile-acid– and ROS–driven injury by rebalancing FXR–SHP–CYP7A1 and NAC redox buffers. These findings propose NAC to be an adjunct with amoxicillin–clavulanate hepatotoxicity to lessen drug-induced liver injury, which remains to be validated clinically for dosing, timing, and patient selection.

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Authors' Contributions

All authors contributed to the design, execution, analysis, and interpretation of the study. The first author (HMT) drafted the manuscript. The co-authors (SKM) reviewed and edited the final version. All authors approved the submitted manuscript.

Conflicts of Interest

The authors declare no competing interests related to this study.

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التأثير الواقي للكبد لمادة الأسيتيل سيستئين ضد التغيرات الكيميائية الحيوية في وظائف الكبد المستحدثة بواسطة الأوجمنتين في الجرذان

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المستخلص

الخلفية: يُعد الأوجمنتين مضادًا حيويًا شائعًا يمكن أن يسبب أذية كبدية؛ إذ يزيد الإجهاد التأكسدي ويُتلِف الخلايا الكبدية. يُعرَف إن-أسيتيل سيستئين (NAC) بخصائصه المضادة للأكسدة وتأثيراته الوقائية على الكبد. هدفت هذه الدراسة إلى تقويم الدور الوقائي لـNAC ضد الأذية الكبدية المحرَّضة بالأوجمنتين في الجرذان من خلال قياس المؤشرات الكيميائية الحيوية، ومؤشرات الإجهاد التأكسدي، وبروفايل الدهون، والنسج المرضية. **المنهجية:** قُسِّم أربعون جرذًا ذكرًا إلى أربع مجموعات (١٠ لكل مجموعة). تلقت المجموعة الضابطة حميةً قاعدية. تلقت مجموعة T1 الأوجمنتين (٣٠ ملغم/كغم/يوم). تلقت مجموعة T2 إن-أسيتيل سيستئين (١٥٠ ملغم/كغم/يوم). تلقت مجموعة T3 إن-أسيتيل سيستئين مع الأوجمنتين بالجرعات نفسها. استمرت المعالجات الفموية لمدة ٥ أسابيع. جُمعت عينات الدم للاختبارات الكيميائية الحيوية (إنزيمات وظائف الكبد وبروفايل الدهون). **النتائج:** سبَّب الأوجمنتين (T1) ارتفاعًا معنويًا في إنزيمات الكبد مقارنةً بالضابطة ($p < 0.05$). وارتفعت أيضًا بشكل معنوي كولسترول المصل وثلاثيات الغليسريد وLDL و($p < 0.05$) VLDL. في المقابل انخفضت HDL والألبومين والبروتين الكلي معنويًا مقارنةً بالضابطة ($p < 0.05$). أدّى NAC بمفرده (T2) إلى تصحيح معنوي لهذه التغيرات باتجاه قيم الضبط ($p < 0.05$). كما حقق NAC مع الأوجمنتين (T3) تحسنًا معنويًا في إنزيمات الكبد وبروفايل الدهون والبيليروبين مقتربًا من مستويات الضبط ($p< 0.05$). **الاستنتاجات:** خفّض NAC بفاعلية الأذية الكبدية البيوكيميائية والنسجية المحرَّضة بالأوجمنتين. ويرتبط دوره الوقائي بتأثيراته المضادة للأكسدة والمضادة للالتهاب والمثبّتة لدهون الدم. قد يُؤخذ NAC بعين الاعتبار كعلاج داعم في سمّية الكبد الدوائية.

الكلمات المفتاحية: الأوجمنتين، الأسيتيل سيستئين، الكبد، السمية الكبدية، مضاد أكسدة