http://doi.org/10.25130/tjphs.2026.20.1.4.33.42

IRAQI Academic Scientific Journals

Tikrit Journal of Pharmaceutical Sciences

ISSN: 1815-2716 (print) -- ISSN: 2664-231X (online)

Journal Home Page: https://tjphs.tu.edu.iq -- Email: tjops@tu.edu.iq

TJPHS

Hepatoprotective effects of palmitoleic acid against ketamine-induced hepatotoxicity in an animal model

Farman K. Rafeeq[*1], Zeina A. Al-Thanoon [2]

[1]Department of Pharmacy, Kirkuk Health Directorate, Kirkuk, Iraq
[2]Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq

Keywords:
Drug-induced liver damage,
Hepatoprotection,
Palmitoleic acid,
Omega-7,
Oxidative stress.

Article history:
-Received: 12/06/2026
-Received in revised: 18/06/2026
-Accepted: 25/06/2026
-Available online: 30/06/2026

***Corresponding author:**
Farman K. Rafeeq
farman.24php11@student.uomosul.edu.iq

Citation:
Rafeeq F K, Z, Al-Thanoon Z A. Hepatoprotective effects of palmitoleic acid against ketamine-induced hepatotoxicity in an animal model. Tikrit J. Pharm. Sci. 2026; 20(1):33-42. *http://doi.org/10.25130/tjphs.2026.20.1.4.33.42*

Abstract

Background: Palmitoleic acid has cytoprotective effects against different insults. This study examined the protective benefits of palmitoleic acid against ketamine-induced hepatic damage in rats by biochemical and histological evaluations.

Methods: In the current study, thirty-six albino male gender rats aged 12-14 weeks were used and divided into four equal groups, each with nine rats: Control, Ketamine, Palmitoleic acid only, and Palmitoleic acid + ketamine. Palmitoleic acid was given orally by gavage at a dosage of 300mg/kg/day for seven days consecutively. On days 8 & 9, ketamine was injected intraperitoneally at a dosage of 160mg/kg/day. Haematoxylin and eosin staining was employed to examine liver tissues microscopically. Additionally, serum liver enzymes were evaluated, such as gamma-glutamyl transferase (GGT) level, alanine aminotransferase (ALT) level, and aspartate aminotransferase (AST) level.

Results: In comparison to the control, the injection of ketamine caused significant elevations in serum ALT (65.41±8.74U/L), AST (153.97±20.65U/L), and GGT (3.36±0.53U/L) ($p < 0.001$). This suggests that the liver damage was substantial. Histopathological analysis of the ketamine-treated cohort demonstrated oncotic and coagulative necrosis, widespread hydropic degeneration, pronounced inflammatory cell infiltration, and vascular congestion. Palmitoleic acid pretreatment greatly mitigated these alterations, lowering ALT, AST, and GGT levels to near-control values and substantially enhancing hepatic histoarchitecture, with very slight residual inflammatory infiltration and minimal degenerative effects.

Conclusions: The findings of this study demonstrated that both histopathological and biochemical manifestations that were induced following ketamine administration have been attenuated by using palmitoleic acid as prophylaxis. This indicates that palmitoleic acid could show marked protective effects against ketamine-induced liver damage in rats.

التأثيرات الوقائية لحمض البالميتوليك على الكبد ضد سمية الكيتامين في نموذج حيواني

فرمان كاكه رش رفيق*[1]، زينة عبد المنعم الذنون[2]

[1] قسم الصيدلة، دائرة صحة كركوك، كركوك، العراق.
[2] قسم علم الأدوية والسموم، كلية الصيدلة، جامعة الموصل، الموصل، العراق.

الخلاصة:
حامض بالميتوليك لديه تأثيرات واقية للخلايا ضد مختلف الأضرار. هذه الدراسة فحصت الفوائد الوقائية للحمض بالميتوليك بجرعة عالية ضد الضرر الكبدي الناتج عن الكيتامين في الجرذان عبر التقييمات الكيميائية الحيوية والنسيجية. في الدراسة الحالية، تم استخدام ستة وثلاثين جرذ أبيض من الذكور بعمر ١٢-١٤ أسبوعًا وتم تقسيمهم إلى أربع مجموعات متساوية، كل مجموعة تحتوي على تسعة جرذان: الضبط، الكيتامين، حامض بالميتوليك فقط، وحامض بالميتوليك + كيتامين. تم إعطاء حامض بالميتوليك عن طريق الفم باستخدام الجوفة بجرعة ٣٠٠ ملغ/كغ/يوم لمدة سبعة أيام متتالية. في اليومين الثامن والتاسع، تم حقن الكيتامين عبر الحقن داخل الصفاق بجرعة ١٦٠ ملغ/كغ/يوم. تم استخدام صبغة الهيماتوكسيلين والإيوزين لفحص أنسجة الكبد مجهريًا. بالإضافة إلى ذلك، تم تقييم إنزيمات الكبد في المصل، مثل مستوى ناقلة غاما جلوتاميل (GGT)، مستوى ناقلة ألانين أمينوترانسفيراز (ALT)، ومستوى أسبارتات أمينوترانسفيراز (AST). مقارنة بالمجموعة الضابطة، تسبب حقن الكيتامين في ارتفاع ملحوظ في مستويات ALT في المصل (٦٥,٤١±٨,٧٤ وحدة/ل)، وAST (١٥٣,٩٧±٢٠,٦٥ وحدة/ل)، وGGT (٣,٣٦±٠,٥٣ وحدة/ل) ($p < 0.001$). هذا يشير إلى أن تلف الكبد كان كبيرًا. أظهر التحليل النسجي للمجموعة المعالجة بالكيتامين نخرًا تأكليًا وتخثرًا، وتوسعًا مائيًا واسعًا، وتسللًا ملحوظًا للخلايا الالتهابية، واحتقانًا وعائيًا. أدى العلاج المسبق بحمض بالميتولييك عالي الجرعة إلى التخفيف الكبير من هذه التغيرات، مما خفض مستويات ALT وAST وGGT إلى قيم قريبة من الضابطة وعزز بشكل كبير البنية النسيجية للكبد، مع تسلل التهابي طفيف جدًا وتأثيرات تنكسية قليلة للغاية. أظهر حمض بالميتولييك عالي الجرعة تأثيرًا وقائيًا ملحوظًا ضد تلف الكبد الناجم عن الكيتامين في الفئران. تشير هذه النتائج إلى أن حمض بالميتولييك يخفف كلًا من مظاهر التلف النسجي والمظاهر الكيميائية الحيوية لتلف الكبد الناتج عن الكيتامين

الكلمات المفتاحية: الضرر الكبدي المستحث بالأدوية، الحماية الكبدية، حمض البالميتولييك، أوميغا-٧، الإجهاد التأكسدي.

INTRODUCTION

There are many concerns in clinical medicine and experimental pharmacology; one of the major concerns is Drug-induced liver injury (DILI) because it is associated with therapy interruption, drug development complications, and progression to acute liver failure [(1)]. Hepatic injury can be assessed using biochemical markers such as measurement of gamma-glutamyl transferase (GGT) level, alanine aminotransferase (ALT) level, and aspartate aminotransferase (AST) level; these markers are among the most widely used indicators in hepatotoxicity studies. Hepatobiliary disturbance is usually evaluated by using GGT as a marker, while both ALT and AST are widely interpreted as markers of hepatocellular injury [(2-4)]. In the evaluation of liver damage, histopathological examination is also an important complementary tool because biochemical abnormalities alone do not fully define the pattern and severity of hepatic injury [(4,5)].

Ketamine is a widely used an aesthetic agent, also used for analgesia, procedural sedation, and certain psychiatric indications [(6)]. However, there are many therapeutic applications of ketamine; hepatic and biliary injury may occur following prolonged or repeated use of ketamine [(6,7)]. Cholangiopathy, abnormal liver function, and cholestatic liver injury, as demonstrated in clinical and observational studies, are linked to substantial ketamine exposure, particularly in critically ill patients [(7,8)]. Supporting the use of ketamine-induced hepatic injury as an experimental model with these observations highlights the importance of evaluating potential hepatoprotective interventions [(9)]. As mentioned before, utilising both histopathological examinations along with biochemical markers is necessary in experimental hepatotoxicity studies, because they provide complementary information on functional and structural liver injury [(4,5)]. Increasing attention toward palmitoleic acid, also known as omega-7 fatty acids, has been linked to its metabolic and immunomodulatory effects [(10)]. Hepatotoxicity studies in mouse models have demonstrated that palmitoleic acid can improve biochemical markers and mitigate histopathological alterations. According to recent studies, palmitoleic acid can exert hepatoprotective effects through altering lipid metabolism, inflammatory pathways and cellular stress responses [(11-13)]. Additionally, there is experimental evidence reporting that omega-7, palmitoleic acid, exhibited a hepatoprotective effect

against toxin-induced liver damage in rats [14]. However, the potential hepatoprotective effects of omega-7 in ketamine-induced liver toxicity are not sufficiently described, particularly with the use of biochemical and histological findings together. Therefore, this study evaluated the hepatoprotective effects of palmitoleic acid against ketamine-induced liver injury in rats using biochemical and histopathological assessments.

METHODS

Experimental animals

This study included thirty-six adult albino rats of male gender weighing around 185-205g and aged 12-14 weeks. The animals were housed under standard laboratory environments with controlled, constant humidity and temperature, along with dark/light cycle of 12 hours. The rats were allowed to access water and diet freely. The procedures of the experiment involving animals were reviewed and approved by the Pharmaceutical Research Ethics Committee (PREC), College of Pharmacy, Mosul University, Mosul, Iraq (Approval code: PREC-25-1-16; approved on November 16, 2025).

Experimental groups

The animals were arbitrarily allocated to four groups (each group consists of 9 rats):

C group: Rats received the vehicle by oral gavage for seven consecutive days.

K group: Rats received the oral vehicle for seven consecutive days, followed by ketamine 160 mg/kg/day intraperitoneally on days 8 and 9 (15,16).

PA group: Rats received palmitoleic acid orally at a dose of 300 mg/kg/day for seven consecutive days.

PAK group: Rats received palmitoleic acid orally at a dose of 300 mg/kg/day for 7 consecutive days, followed by intraperitoneal ketamine at a dose of 160 mg/kg/day on days 8 and 9 [15,16].

Sample collection

On day 10, after anaesthesia, blood samples were obtained from rats using heart puncture. Serum for biochemical examination was obtained by centrifuging the samples at 3000 rpm for 15 minutes after clot formation. The liver tissues were collected from the animals, washed using cold normal saline, and embedded in neutral buffered formalin (10%) for histological analysis.

Chemicals and reagents

Ketamine hydrochloride (50 mg/mL, injectable solution) was procured from Panpharma GmbH, Germany. Palmitoleic acid (omega-7; cis-16:1 n-7) was delivered by Provinal® Purified Omega-7 softgel capsules (Life Extension®, Fort Lauderdale, FL, USA), each containing 210 mg of palmitoleic acid. The contents of the soft gel capsules were removed for oral administration. The commercial colourimetric assays (REF 92027 and 92025) were used to measure serum ALT and AST activities. The GAMMA GT carboxy-GPNA colourimetric kit (REF 81110) was used to measure GGT activity. All of these kits were provided by BIOLABO S.A.S., France and followed the manufacturer's instructions. Olive oil was used as an oral vehicle and also for diluting palmitoleic acid due to the lipophilic nature of palmitoleic acid; this method is well-established in rodent pharmacological models for hydrophobic compounds [17].

Histopathological examination

The neutral buffered formalin of 10% concentration was used for fixing liver tissue samples and paraffin for embedding them. Haematoxylin & Eosin (H&E) was used to stain the liver sample slices that were 4 to 5 micrometres thick. The light microscope was used to examine liver sections. A pathologist who was blinded to experimental groups performed histopathological evaluation to assess degeneration of hepatocytes, necrosis and inflammation. Hepatic injury was scored semi-quantitatively for key features: necrosis (0-4), inflammatory cell infiltration (0-3), steatosis (0-3), and sinusoidal congestion (0-3).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to compare differences among groups. A P value < 0.05 was considered statistically significant. A post hoc power analysis was performed using G*Power software (version 3.1.9.7; Heinrich Heine University Düsseldorf, Germany). Based on a one-way ANOVA with four experimental groups, a total sample size of 36 animals, and $\alpha = 0.05$, the observed effect size for serum ALT activity (Cohen's $f = 1.90$) yielded an achieved statistical power ($1 - \beta$) greater than 0.999, indicating that the study was adequately powered to detect differences among the experimental groups.

RESULTS

Weight changes in the studied group

In general, body weight was not markedly affected by the experimental treatments, and all groups continued to gain weight during the study period. Although the ketamine-treated group showed a relatively lower increase in body weight than the other groups, this difference was not statistically significant and may be related to transient effects of ketamine exposure, such as reduced food intake following anesthesia.

Overall, the findings suggest that the treatments did not cause significant adverse effects on body-weight progression during the experimental period (Table 1).

Table (1): Rat body weight in the study groups.

Rat body weight		
Groups	**Before**	**After**
C	188±5.6	198±5.3
K	195±6.5	201±4.8
PA	189±5.2	200±5.4
PAK	190±5.6	202±4.7

Liver enzyme changes in the studied group

Serum ALT levels: The ketamine-treated group showed a significant elevation in serum ALT levels in comparison to the control group. In contrast, pretreatment with palmitoleic acid (300 mg/kg/day) in the PAK group significantly lowered the serum ALT levels compared to the ketamine group and restored them to near-control values. ALT levels in the palmitoleic acid-only group didn't show a significant difference when compared to the control (Table 2, Table 3, and Figure 1).

Serum AST levels: The serum AST levels also showed significant elevation in the ketamine-treated group compared to the control group. Regarding the PAK group, pretreatment with palmitoleic acid significantly attenuated this increase, and AST levels in the palmitoleic acid-only group did not show a significant difference from those in the control group (Table 2, Table 3, and Figure 2).

Serum GGT levels: Serum GGT levels were markedly increased after ketamine injections in the ketamine group compared to those in the control group. Pretreating with palmitoleic acid in the PAK group significantly reduced GGT relative to the ketamine-treated group and restored values to a level comparable with control. No statistically significant differences in the serum GGT levels were seen between the palmitoleic acid group and the control group (Table 2, Table 3, and Figure 3).

Table (2): Serum liver enzyme levels in the study groups (mean ± SD)

Groups	ALT (U/L)	AST (U/L)	GGT (U/L)
C	40.00±5.67	95.49±17.87	2.28±0.43
K	65.41±8.74	153.97±20.65	3.36±0.54
PA	41.08±5.25	96.76±15.43	2.34±0.41
PAK	41.67±4.74	98.68±13.50	2.38±0.56
P value	0.0001	0.0001	0.0001

Table (3): Post hoc analysis of measured serum liver enzymes in the studied groups.

groups	ALT (U/L)	AST (U/L)	GGT (U/L)
C vs K	0.00001	0.00001	0.0003
c vs PA	0.9832	0.9986	0.9937
c vs PAK	0.9424	0.9785	0.9723
K vs PA	0.00001	0.00001	0.0006
K vs PAK	0.00001	0.00001	0.0010
PA vs PAK	0.9972	0.9951	0.9981
Data represent p-values after post hoc analysis following one way ANOVA at 95% CI			

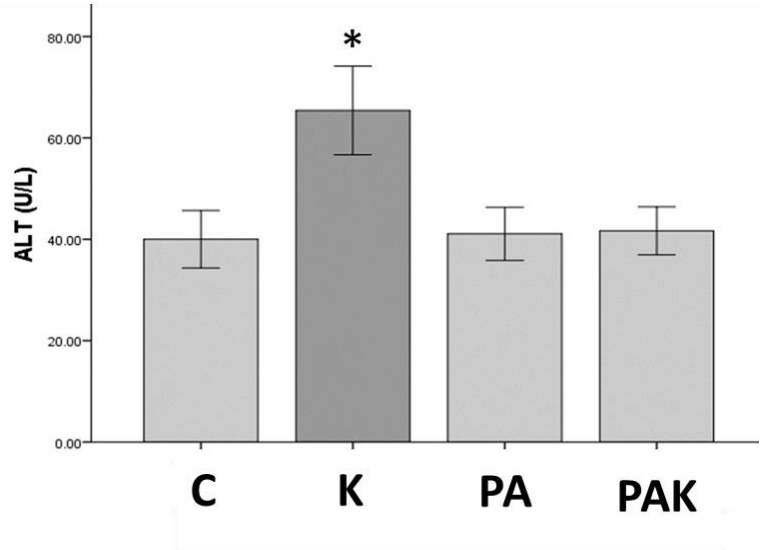
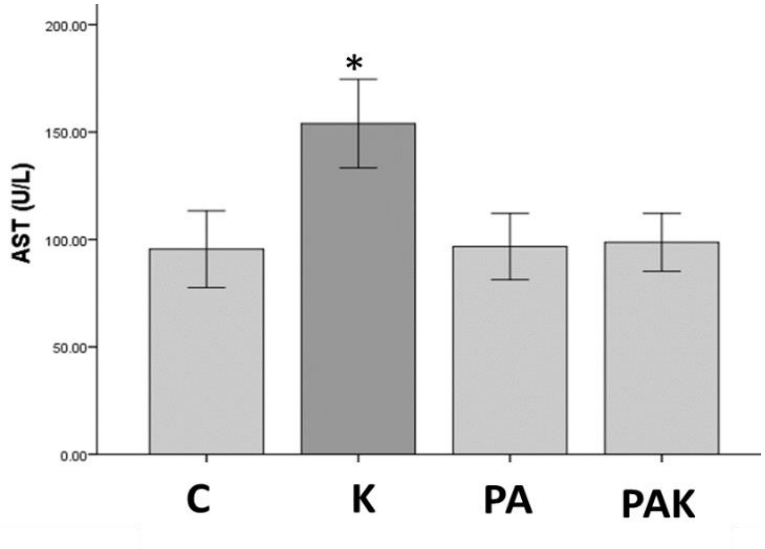


Figure (1): Serum alanine aminotransferase (ALT) levels across the experimental groups. Data are presented as mean ± SD (n = 9 per group). * Indicates that ketamine injections markedly elevated the ALT level in comparison to other groups. Palmitoleic acid pretreatment restored the level of ALT to near-normal value of the control.



Figure(2): Serum aspartate aminotransferase (AST) levels across the experimental groups. Data are presented as mean ± SD (9 rats per group). * Indicates that the ketamine-treated group showed significantly higher levels of serum AST compared to other groups. Palmitoleic acid pretreatment restored the level of AST to near-normal values of the control.

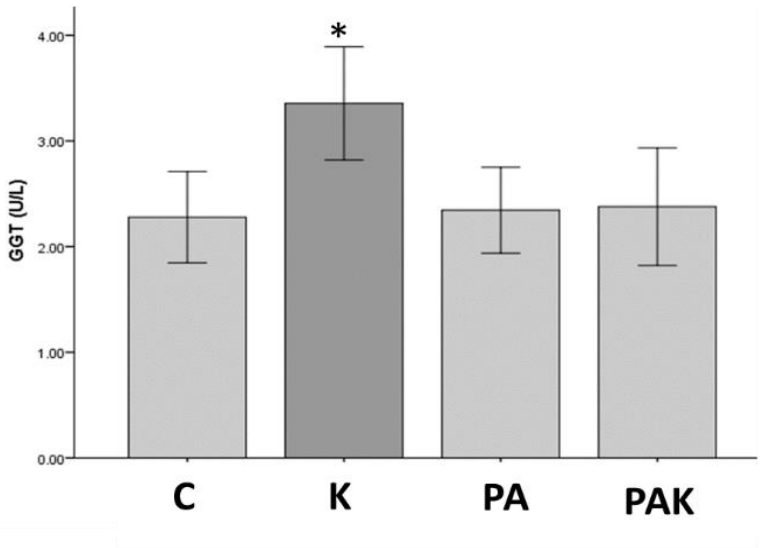


Figure (3): Serum gamma-glutamyl transferase (GGT) levels across the experimental groups. Data are presented as mean ± SD (number of rats in each group is 9). * Indicates that GGT levels were increased markedly in the ketamine-treated group compared to other groups. Pretreatment with palmitoleic acid restored the level of GGT to near-normal values of the control.

Histopathological findings

Histopathological examination supported the biochemical findings. Normal sinusoidal, portal and central venous structures with normal hepatic architecture and intact hepatocytes are seen in liver sections from the control group and palmitoleic acid-only groups. In contrast, marked liver injury is seen in rat liver sections from the ketamine-treated group; the hepatic injury from this group is characterised by vascular congestion, severe inflammatory-cell infiltration, oncotic and coagulative necrosis, and diffuse hydropic degeneration. In the PAK group, pretreatment with palmitoleic acid markedly attenuated these abnormalities, with liver sections showing largely preserved hepatic architecture, mostly intact hepatocytes, and only mild residual inflammatory infiltration, mild vascular congestion, and minimal degenerative change compared with the ketamine group (Figure 4 and Figure 5).

The ketamine-treated group exhibited the greatest hepatic injury, characterised by severe necrosis, dense inflammatory infiltration, and marked vascular congestion, resulting in the highest composite injury score (10/13). In contrast, both the control and palmitoleic acid-only groups showed essentially normal liver architecture without detectable pathological alterations (0/13). Pretreatment with palmitoleic acid markedly ameliorated ketamine-induced hepatic damage, reducing necrosis, inflammatory infiltration, and sinusoidal congestion to mild levels (3/13), while no steatosis was observed in any experimental group (Table 4).

DISCUSSION

The present study showed that ketamine caused clear liver injury in rats, as reflected by marked increases in ALT, AST, and GGT, together with histopathological findings of hepatocellular degeneration, necrosis, inflammatory-cell infiltration, and vascular congestion. These findings are consistent with previous animal studies, which have demonstrated that ketamine can induce liver injury and elevate serum liver enzymes when used in high doses or repeatedly [9,18,19]. Additionally, the ketamine-induced liver injury, in experimental models, may be related to oxidative injury [20]. In general, body weight was not markedly affected by the experimental treatments, and all groups continued to gain weight during the study period, indicating normal growth.

The interesting point in the current study is that besides elevations in both AST and ALT levels, which indicate hepatocellular injury, ketamine also increased the GGT levels, suggesting hepatobiliary injury. This finding is relevant to previous studies that ketamine exposure has increasingly been associated with cholestatic liver injury and cholangiopathy in human studies [7,21-24]. As described by recent reviews, the complications of subsequent ketamine-related hepatotoxicity range from mild biochemical abnormalities to more serious biliary injury [25].

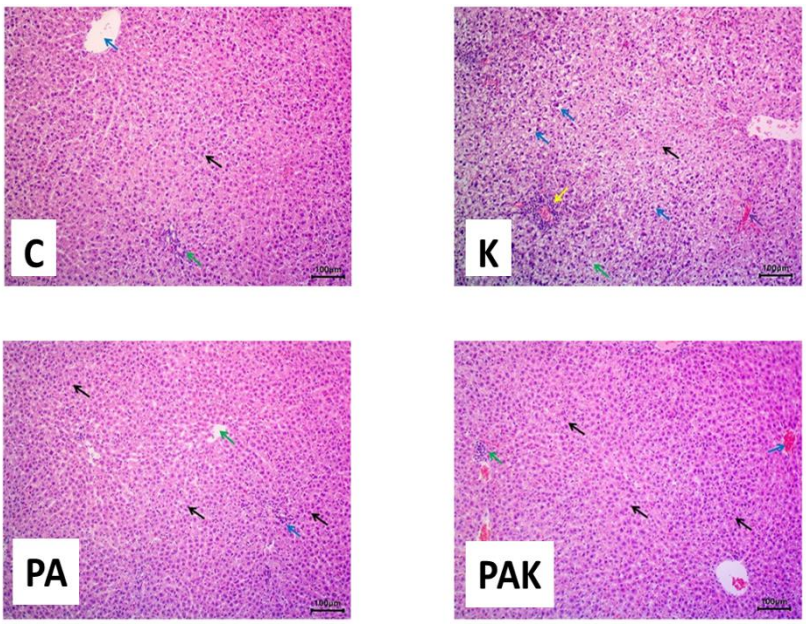


Figure (4): Representative photomicrographs of liver sections stained with hematoxylin and eosin (H&E) (100×). The control group shows normal hepatic architecture with intact hepatocytes and preserved vascular and portal structures; the ketamine group shows marked hepatic injury with hepatocellular degeneration, necrosis, inflammatory-cell infiltration, and vascular congestion; The palmitoleic acid-only group shows preserved hepatic architecture comparable to the control group; the palmitoleic acid + ketamine group shows marked histological improvement with near-normal hepatic architecture and reduced inflammatory and degenerative changes.

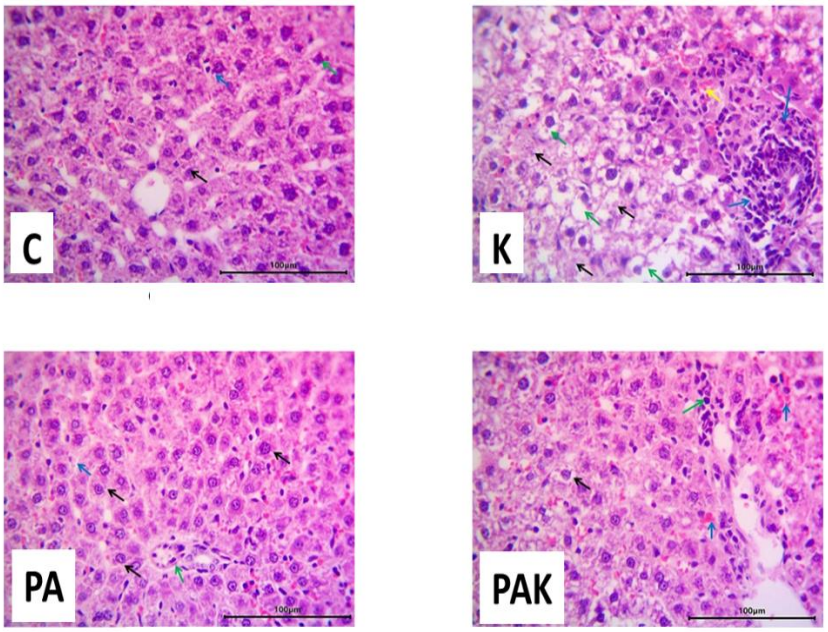


Figure (5): Representative photomicrographs of liver sections stained with hematoxylin and eosin (H&E) (400×). The control group show normal hepatocyte morphology; the Ketamine group shows oncotic necrosis, diffuse hydropic degeneration, inflammatory-cell infiltration, and vascular congestion; the Palmitoleic acid group shows normal hepatocyte morphology without obvious pathological alterations; Palmitoleic acid+ ketamine shows preserved hepatocyte morphology with only mild residual inflammatory infiltration and mild vascular congestion.

Table (4): Semi-quantitative histopathological liver injury score estimated from representative images.

Group	Necrosis (0–4)	Inflammatory Cell Infiltration (0–3)	Steatosis (0–3)	Sinusoidal Congestion (0–3)
C	0	0	0	0
K	4	3	0	3
PA	0	0	0	0
PAK	1	1	0	1

Critically ill patients showed progressive cholangiopathy and cholestatic liver injury following intravenous ketamine administration [8,26], and even after discontinuation, there was persistent ketamine-induced cholangiopathy [27]. The biochemical findings of the study were strengthened by the previous findings.

Another point of interest, which is also considered a major finding, is the attenuation of ketamine-induced liver toxicity by pretreatment with palmitoleic acid. The PAK group palmitoleic acid + ketamine) showed a marked decline in serum levels of ALT, AST, and GGT, which have returned to near normal values, and liver histology showed substantial preservation of hepatic architecture. However, there is no study which directly assesses the potential effects of palmitoleic acid in ketamine-induced hepatotoxicity, but previous studies support the role of palmitoleic acid as a hepatoprotective agent in other liver-related settings [12, 28-30]. The hepatoprotective effect of palmitoleic acid is again supported as it improves metabolic function in fatty liver through PPARα-dependent AMPK activation [31].

Palmitoleic acid has a multifactorial protective role, as suggested by experimental studies; palmitoleic acid can enhance and regulate metabolic functions of hepatocytes, suppress inflammatory signals and also modulate cellular stress [12,29,32,33]. Oxidative stress and ferroptosis-related pathways in liver disease are also influenced by palmitoleic acid, as shown in a recent work [10,11,13]. Another contribution to the protective profile of palmitoleic acid in fatty liver is through the AMPK- and PPARα-related effects [31]. The improvement in the histopathological and biochemical findings in the present study, which is seen following pretreatment with palmitoleic acid, is compatible with previously described mechanisms even though these mechanisms are not measured directly in this work.

Regarding the palmitoleic acid group and the palmitoleic acid-only group, the administration of palmitoleic acid alone at a dose of 300mg/ kg/day has not been linked to histological or biochemical abnormalities, and this supports the safety and tolerability of palmitoleic acid at the given dose. Despite the promising findings in the current work, there are also limitations, including that only male rats were used, skipping the hormonal effects seen in female rats, and a lack of assessment of mechanistic biomarkers such as TNF-α, IL-6, MDA and bile-acid-related markers. Further studies are required to describe the dose-response relationships and molecular mechanisms underlying its protective effect against ketamine-induced liver injury.

CONCLUSION

In conclusion, we found that palmitoleic acid has valuable effects in protecting the rat's liver from damage resulting from ketamine exposure. The protective effects of palmitoleic acid were documented through modification of the serum GGT, AST and ALT levels and significant improvement in histopathological abnormalities. To fully understand the mechanism of action at a molecular level and to investigate wider applications of palmitoleic acid, further research is needed.

CONFLICT OF INTEREST

The author(s) declare no conflict of interest, financial or otherwise.

Funding

No funding was received for conducting this study.

REFERENCES

1. Saleh AK, El-Masry TA, El-Kadem AH, Ashour NA, El-Mahdy NA. Exploring drug-induced liver injury: comprehensive insights into mechanisms and management of hepatotoxic agents. *Future Journal of Pharmaceutical Sciences*. 2025;11(1):38-46. doi:10.1186/s43094-025-00788-5.
2. Andrade RJ, Aithal GP, Björnsson ES, Kaplowitz N, Kullak-Ublick GA, Larrey D, et al. EASL Clinical Practice Guidelines: Drug-induced liver

injury. *Journal of hepatology*. 2019;70(6):1222–61. doi:10.1016/j.jhep.2019.02.014.
3. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *American Journal of Gastroenterology*. 2021;116(5):878–98. doi:10.14309/ajg.0000000000001259.
4. Kleiner DE. The histopathological evaluation of drug-induced liver injury. *Histopathology*. 2017;70(1):81–93. doi:10.1111/his.13082.
5. Ahmad J, Barnhart HX, Bonacini M, Ghabril M, Hayashi PH, Odin JA, et al. Value of liver biopsy in the diagnosis of drug-induced liver injury. *Journal of hepatology*. 2022;76(5):1070–8. doi:10.1016/j.jhep.2021.12.043.
6. Thakkar B, Wu GY. Ketamine hepatotoxicity: an underappreciated cause of liver damage-analysis by RUCAM. *Journal of Clinical and Translational Hepatology*. 2025;13(6):524-533. doi:10.14218/JCTH.2024.00478.
7. De Tymowski C, Dépret F, Dudoignon E, Moreno N, Zagdanski AM, Hodjat K, et al. Ketamine restriction correlates with reduced cholestatic liver injury and improved outcomes in critically ill patients with burn injury. *JHEP Reports*. 2024;6(2):100950. doi:10.1080/14659891.2026.2679106.
8. Mallet V, Bock K, Mandengue PD, Dufour N, Voigtlaender T, Ricard JD, et al. Intravenous ketamine and progressive cholangiopathy in COVID-19 patients. *Journal of hepatology*. 2021;74(5):1243–4. doi:10.1016/j.jhep.2021.02.007.
9. Chen X, Zhang Z, Shen M, Ma X, Qiu D, Li S, et al. Downregulation of the NLRP3/Caspse-1 Pathway Ameliorates Ketamine-Induced Liver Injury and Inflammation in Developing Rats. *Molecules*. 2022;27(9):2931. doi:10.3390/molecules27092931.
10. Bermúdez MA, Pereira L, Fraile C, Valerio L, Balboa MA, Balsinde J. Roles of Palmitoleic Acid and Its Positional Isomers, Hypogeic and Sapienic Acids, in Inflammation, Metabolic Diseases and Cancer. *Cells*. 2022;11(14):2146. doi:10.3390/cells11142146.
11. Wang H, Shan C, Guo G, Ning D, Miao F. Therapeutic potential of palmitoleic acid in non-alcoholic fatty liver disease: Targeting ferroptosis and lipid metabolism disorders. *International Immunopharmacology*. 2024;142:113025. doi:10.1016/j.intimp.2024.113025.
12. Souza CO, Teixeira AA, Biondo LA, Silveira LS, de Souza Breda CN, Braga TT, et al. Palmitoleic acid reduces high fat diet-induced liver inflammation by promoting PPAR-γ-independent M2a polarization of myeloid cells. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*. 2020;1865(10):158776. doi:10.1016/j.bbalip.2020.158776.
13. Han Q, Liu Y, Liu X, Geng Y, Wu Q, Xiao H. Palmitoleic acid inhibits hepatotoxic effects by reducing trimethylamine-n-oxide (TMAO) formation in high l-carnitine-treated mice. *Nutrients*. 2024;16(21):3599. doi:10.3390/nu16213599.
14. Hameed HA, Hassan AF. The prophylactic anti-inflammatory effect of omega-7 against paracetamol-induced liver injury in rats. *The Iraqi Journal of Veterinary Medicine*. 2022 Dec 28;46(2):43-7. doi:10.30539/ijvm.v46i2.1412.
15. Wahdan RAM, Ali MS, Moustafa MMI, Mohammed Hassan MZ. Effects of Single Dose of Intraperitoneal Ketamine on the Liver of Adult Male Albino Rats: Histological and Immunohistochemical Study. J Cytol Histol. 2024;15(4): 1-4. doi:10.37421/2157-7099.2024.15.753.
16. Hameed HA, Hassan AF. The Hepatoprotective Effect of Omega-7 Against Paracetamol-Induced Hepatotoxicity in Male Rats. Iraqi Journal of Pharmaceutical Sciences. 2023 Dec 30;32(3):85-94. doi:10.31351/vol32iss3pp85-94
17. Shah KN, Jadhav S, Patel M, Jikadara J, Modi N. Effect of Vehicles on the Functional Observational Battery by Oral Gavage Administration in Wistar Rats and Need for Historical Control Data. Indian J Pharm Sci. 2024;86(3). doi:10.36468/pharmaceutical-sciences.1355
18. Kalkan Y, Tomak Y, Altuner D, Tumkaya L, Bostan H, Yilmaz A, et al. Hepatic effects of ketamine administration for 2 weeks in rats. *Human and experimental toxicology*. 2014;33(1):32–40. doi:10.1177/0960327112472990.
19. Bedir Z, Ozkaloglu Erdem KT, Ates I, Olmezturk Karakurt TC, Gursul C, Onk D, et al. Effects of ketamine, thiopental and their combination on the rat liver: A biochemical evaluation. *Advances in Clinical and Experimental Medicine*. 2021;31(3):285–92. doi:10.17219/acem/143573.
20. Schimites PI, Segat HJ, Teixeira LG, Martins LR, Mangini LT, Baccin PS, et al. Gallic acid prevents ketamine-induced oxidative damages in brain regions and liver of rats. *Neuroscience letters*. 2020;714:134560. doi:10.1016/j.neulet.2019.134560.

21. Teymouri A, Nasoori H, Fakheri M, Nasiri A. Features of biliary tract diseases in ketamine abusers: a systematic review of case reports. *Journal of medical case reports*. 2024;18(1):84. doi:10.1186/s13256-024-04421-6.
22. Chun J, Kotha S, Nayagam J, Gallaher C, Miquel R, Hong S, et al. Ketamine cholangiopathy: clinical features and liver biopsy findings. *Histopathology*. 2025;87(1):130–7. doi:10.1111/his.15435.
23. Bartoli A, Cursaro C, Seferi H, Andreone P. Secondary sclerosing cholangitis after SARS-CoV2: ICU ketamine use or virus-specific biliary tropism and injury in the context of biliary ischemia in critically ill patients?. *Hepatic Medicine: Evidence and Research*. 2023:93-112. doi:10.2147/HMER.S384220.
24. Yoo N, Thomas S, Bender M, Cheng XJC. A Case of Hepatotoxicity Induced by Therapeutic Ketamine Use for Sedation. *Case Reports in Critical Care*. 2024;2024(1). doi:10.1155/2024/8366034.
25. Waheed HW, Ashraf MR, Sajjad T, Jehangir H, Baig I, Zulaid A, et al. Hepatobiliary Complications Associated With Ketamine Use: Clinical Insights and Future Directions. *Cureus*. 2025. doi:10.7759/cureus.84974.
26. Wendel-Garcia PD, Erlebach R, Hofmaenner DA, Camen G, Schuepbach RA, Jüngst C, et al. Long-term ketamine infusion-induced cholestatic liver injury in COVID-19-associated acute respiratory distress syndrome. *Critical Care*. 2022;26(1):148. doi:10.1186/s13054-022-04019-8.
27. Nyirenda TJ, Shirazi-Nejad A, Soliman AS. Persistent Ketamine-Induced Cholangiopathy: An Approach to Management. *Cureus*. 2020. doi:10.7759/cureus.11611.
28. Yang ZH, Miyahara H, Hatanaka A. Chronic administration of palmitoleic acid reduces insulin resistance and hepatic lipid accumulation in KK-Ay Mice with genetic type 2 diabetes. Lipids in Health and disease. 2011;10(1):120. doi:10.1186/1476-511X-10-120.
29. Souza CO, Teixeira AAS, Lima EA, Batatinha HAP, Gomes LM, Carvalho-Silva M, et al. Palmitoleic Acid (N-7) Attenuates the Immunometabolic Disturbances Caused by a High-Fat Diet Independently of PPAR α. Mediators of inflammation. 2014;2014:1–12. doi:10.1155/2014/582197.
30. Cruz MM, Simão JJ, Sá RDCC de, Farias TSM, Silva VS da, Abdala F, et al. Palmitoleic Acid Decreases Non-alcoholic Hepatic Steatosis and Increases Lipogenesis and Fatty Acid Oxidation in Adipose Tissue From Obese Mice. *Frontiers in endocrinology*. 2020;11. doi:10.3389/fendo.2020.537061.
31. de Souza CO, Teixeira AAS, Biondo LA, Lima Junior EA, Batatinha HAP, Rosa Neto JC. Palmitoleic Acid Improves Metabolic Functions in Fatty Liver by PPARα-Dependent AMPK Activation. *Journal of cellular physiology*. 2017;232(8):2168–77. doi:10.1002/jcp.25715.
32. Guo X, Jiang X, Chen K, Liang Q, Zhang S, Zheng J, et al. The Role of Palmitoleic Acid in Regulating Hepatic Gluconeogenesis through SIRT3 in Obese Mice. *Nutrients*. 2022;14(7):1482. doi:10.3390/nu14071482.
33. Zhang J, Zhao M, Yu H, Wang Q, Shen F, Cai H, et al. Palmitoleic Acid Ameliorates Metabolic Disorders and Inflammation by Modulating Gut Microbiota and Serum Metabolites. *Molecular Nutrition & Food Research*. 2024;68(7). doi: 10.1002/mnfr.202300749.