GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 5 (374) Май 2026

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
NO 5 (374) 2026

Содержание:

GEORGIAN MEDICAL NEWS
No 5 (374) 2026

THE POTENTIAL HEPATOPROTECTIVE EFFECT OF PALMITOLEIC ACID AGAINST KETAMINE-INDUCED LIVER INJURY IN RATS: OXIDATIVE, INFLAMMATORY, AND HISTOPATHOLOGICAL EVALUATION

Farman K. Rafeeq[1,2], 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.*

Abstract.

Objective: In this study, the dose-dependent anti-inflammatory, anti-oxidant and histological impacts of palmitoleic acid were evaluated subsequent ketamine-induced liver injury in rats.

Methods: Forty-five adult male albino rats were assigned to five groups (n=9 each): control, ketamine, palmitoleic acid alone, low-dose palmitoleic acid plus ketamine, and high-dose palmitoleic acid plus ketamine. Palmitoleic acid was given orally through the gavage for 7 consecutive days at doses of 100mg/kg/day or 300mg /kg/day. Hepatic injury was induced through injecting ketamine intraperitoneally at dose of 160 mg/kg/day on days 8 and 9, with an interval of 24 hours between injections. Blood and liver samples were collected on day 10 to measure the serum levels of Interleukin-6(IL-6), malondialdehyde (MDA), and tumor necrosis factor-alpha (TNF-α) and histological examination.

Results: In comparison to the control group, the ketamine-treated group showed significantly elevated levels of serum MDA, TNF-α, and IL-6. Hepatic injury has occurred in the ketamine-treated group, which is characterized by degeneration of hepatocytes, significant necrosis, vascular congestion and inflammatory cell infiltration. These histological and biochemical alterations were attenuated by pretreatment with palmitoleic acid in dose dependent pattern.

Conclusion: Palmitoleic acid therapy protects rats' livers against the damage produced by ketamine. This protection was linked to reduced levels of inflammatory cytokines, less oxidative stress, and less damage to tissues. The protection was greatest at higher doses. These data suggest that palmitoleic acid may be an effective supplementary approach to mitigate ketamine-induced liver damage.

Key words. Ketamine, hepatotoxicity, palmitoleic acid-omega-7, oxidative stress, inflammation, hepatoprotection.

Introduction.

One of the challenges in toxicology and clinical medicine is liver injury due to drugs which is known as drug-induced liver injury (DILI), that is characterized by cholestasis, hepatocyte injury, or mixed patterns and may lead to number of illnesses [1,2]. Many types of drug-induced liver damage is through oxidative stress mechanism that can lead to apoptosis, inflammations and mitochondrial malfunctions [3,4].

Ketamine is a dissociative anaesthetic that can be used for a number of medical purposes, such as pain relief, sedation during procedures, and anaesthesia in intensive care units [5-7]. Utilization of ketamine over long period of time can cause liver damage in a way that causes cholestasis. Moreover, people receiving mechanical ventilation have exhibited a correlation between elevated levels of bilirubin and exposure of ketamine in proportion to the dose [8]. A clinical trial also indicated that severely ill burn patients who used a lot of ketamine for a long time were more likely to have cholestatic liver disease and die. Limiting ketamine dosages markedly diminished liver injury and enhanced three-month survival, but other sedatives were not linked to these detrimental effects [9].

Beyond clinical observations, animal studies establish hepatotoxic effects associated with ketamine exposure. In rats, recurrent subanesthetic ketamine administration has been linked to hepatic oxidative stress and inflammation, as evidenced by increased oxidant markers and pro-inflammatory mediators in liver tissue [10]. These findings prop rationalization for evaluating hepatoprotective agents that can alleviate oxidative injury and inflammatory responses in ketamine-induced liver damage [3].

Palmitoleic acid (cis-16:1 n-7), Palmitoleic acid, a monounsaturated fatty acid, is identified as a bioactive compound that is capable to modulate immunometabolic signals rather than only serving as energy substrate [11]. Palmitoleate can influence macrophage activation and anti-inflammatory responses, as demonstrated in experimental studies elucidating the molecular pathways that may contribute to its therapeutic actions in inflammatory tissue injury [12].

Numerous studies support the concept that palmitoleic acid preserves the liver. In a high-fat diet paradigm, palmitoleic acid administration decreased liver inflammation and reoriented hepatic myeloid cells towards an anti-inflammatory phenotype, thereby enhancing an immunomodulatory hepatoprotective mechanism [13]. Additionally, another study with mice shows that palmitoleic acid can improve outcomes related to liver damage in models of liver stress, including the increase of antioxidant-related parameters and functional indicators [14]. Recent technological investigations in NAFLD models suggest that palmitoleic acid may mitigate liver injury and oxidative stress, correlating with lipid metabolism regulation and ferroptosis-related pathways [15].

Despite these findings, the dose -dependent hepatoprotective effects of palmitoleic acid in ketamine-induced liver injury have not been systematically described. Therefore, establishing dose-response relationship is essential in pharmacology and toxicology since it clarifies the effective dose ranges, strengthens causal inference, and improves translational interpretation [1]. Hence, the goal of this work is to evaluate dose-dependent hepatoprotective effects of palmitoleic acid in rats following ketamine -induced liver damage through evaluating oxidative stress, inflammatory markers, and histological alterations.

Materials and Methods.

Reagents and chemicals: Ketamine HCl (50 mg/mL, solution for injection) was obtained from Panpharma GmbH (Germany).

Omega-7 (palmitoleic acid; cis-16:1 n-7) was administered using Provinal® Purified Palmitoleic acid softgel capsules (Life Extension®, Fort Lauderdale, FL, USA), each softgel providing 210 mg palmitoleic acid. The contents of the softgel capsules were extracted and used for administration orally.

Enzyme-linked immunosorbent assay (ELISA) kits for Interleukin-6 (IL-6), Malondialdehyde (MDA), and Tumor necrosis factor-alpha (TNF-α) were purchased from SunLong Biotech Co., Ltd. (China).

Experimental animals: The current study included forty-five 12-week-old male albino rats weighing 180-240 grams. The animals were maintained in a well-controlled animal house with temperature of 22 ± 2 °C, light/dark cycle of 12 hours, and humidity of 50% to 60%, they were provided free access to water and diet and were acclimatized for seven days before the experiment.

Ethical approval: Ethical clearance of all experimental protocols was obtained from the Pharmaceutical Research Ethics Committee (PREC), College of Pharmacy, University of Mosul, Iraq (approval no. PREC-25-1-16; November 16, 2025). All procedures involving animals were carried out according to internationally recognized guidelines regarding use and care of laboratory animals.

Experimental design: A total of forty-five male albino rats were randomly allocated into five groups, with nine rats in each group, as follows:

Group I (a negative control): the rats were given the oral vehicle by gavage for 7 days.

Group II (Ketamine-treated group): oral gavage was used to administer vehicle for 7 consecutive days, and then followed by ketamine injection intraperitoneally at dose (160mg/kg/day) on day8&9 to induce liver injury.

Group III (Palmitoleic acid only group): Rats received oral palmitoleic acid (300 mg/kg/day) through gavage for 7 consecutive days.

Group IV (Low-dose palmitoleic acid + ketamine group): Rats were given palmitoleic acid (100 mg/kg/day) by mouth for7 consecutive days. Then, on days 8 and 9, rats were administered two injections of ketamine (160 mg/kg/day) intraperitoneally, 24 hours apart.

Group V (High-dose palmitoleic acid + ketamine group): Rats were given palmitoleic acid (300 mg/kg/day) by mouth for seven days. Then, on days 8 and 9, rats were administered two injections of ketamine (160 mg/kg/day) intraperitoneally, 24 hours apart.

In this work, the ketamine induction schedule was selected based on preliminary optimization indicating that two doses produced a more consistent and moderate hepatic injury suitable for evaluating protective effects.

Sample collection: On day 10, following anaesthesia, blood samples were obtained through cardiac puncture. The collected blood was permitted to coagulate and thereafter centrifuged at 3000 rpm for 15 minute to isolate serum for biochemical analysis. The animals were then scarified, and the livers were extracted, rinsed with cold normal saline, and prepared for histological analysis.

Histopathological Examination: Neutral buffered formalin (10%) and paraffin were used in fixation and embedding liver tissue samples respectively. The liver sample sections with a thickness of 4 to 5 micrometer were stained using Hematoxylin &Eosin (H&E). 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.

Statistical analysis:

IBM SPSS Statistics (version 22) was used to perform statistical evaluation of data and one-way ANOVA was used to assess differences among groups, after which Tukey's post hoc test was applied for multiple comparisons. The findings were expressed as mean ± standard deviation (SD), and p-value below 0.05 was considered statistically significant.

Results.

The impact of Palmitoleic Acid on Serum Malondialdehyde (MDA) Levels.

Serum MDA levels were estimated as an index of oxidative damage and lipid oxidative degradation. As shown in Table 1 and Figure 1, the ketamine-treated group (Group II) showed significantly higher serum MDA levels in comparison to the control-Group I ($p < 0.001$). Whereas pretreatment with palmitoleic acid at 100 mg/kg/day (Group IV) markedly decreased serum MDA levels compared to Group II (ketamine group). A more pronounced reduction was observed with palmitoleic acid at 300 mg/kg/day (Group V), with MDA levels approaching those of the control. Compared to the control, the palmitoleic acid-only group (Group III) showed no significant differences ($P > 0.05$) indicating the safety and tolerability of palmitoleic acid at dosage of 300mg/kg/day. No significant differences seen between Groups IV &V. These findings indicate a dose-responsive effect of palmitoleic acid which attenuated ketamine-induced oxidative stress.

Effect of Palmitoleic Acid on Inflammatory Cytokines (TNF-α and IL-6).

Inflammatory responses were evaluated by measuring serum levels of inflammatory cytokines (IL-6 &TNF-α). Inflammatory cytokines were markedly elevated after ketamine injection in ketamine-treated group (Group II) in comparison to Group I ($p < 0.001$) as demonstrated in table2 &figure2. While pretreatment with palmitoleic acid (100 mg/kg/day) in Group IV markedly mitigated the elevation of both serum cytokines levels in ketamine-treated Group II ($p < 0.01$). For Group V, a greater reduction in inflammatory cytokines was seen when palmitoleic acid was given at high dose (300 mg/kg/day) before injection of ketamine, cytokine levels of this group approaching those of the Group I. No significant differences were seen between the control group (Group I) and the palmitoleic acid-only group (Group III). These results demonstrate dose-dependent anti-inflammatory effects of palmitoleic acid in ketamine-induced liver injury (Table 2 and Figures 2 and 3).

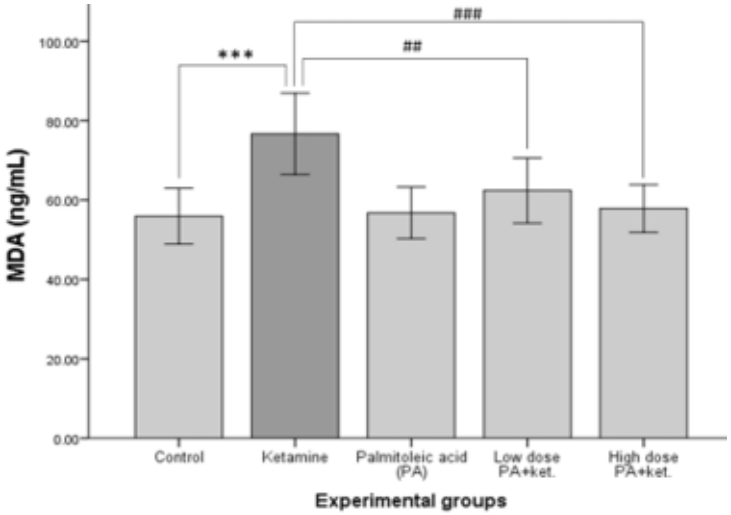

Figure 1. *Serum MDA level across the experimental groups. The data are presented as Mean ± SD (n=9 in each group). Serum MDA level rose greatly after ketamine exposure, while pretreatment with palmitoleic acid lowered this increase markedly at both tested doses. ***p < 0.001 vs control group; ##p < 0.01 and ###p < 0.001 vs ketamine group.*

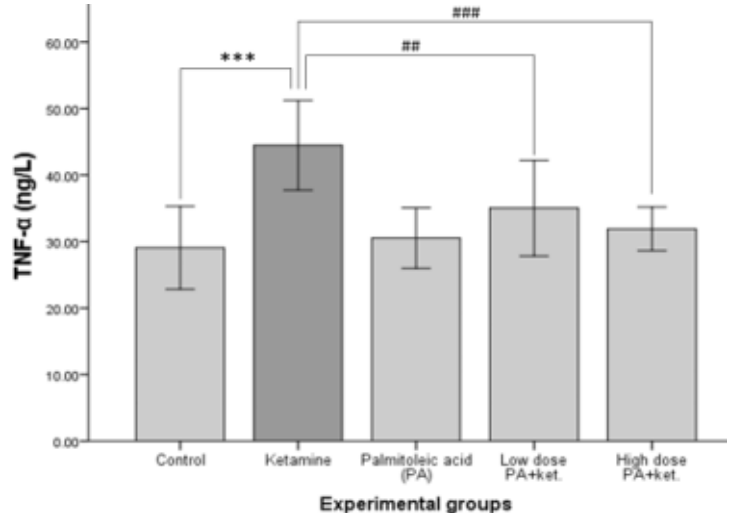

Figure 2. *Serum TNF-alpha level among experimental groups. The data were presented as Mean ± SD (n=9/group). The injection of ketamine markedly elevated serum TNF-α level in comparison to Control group, whereas pretreatment with palmitoleic acid attenuated this increase in both tested doses. ***p < 0.001 versus control group; ##p < 0.01 and ###p < 0.001 versus ketamine group.*

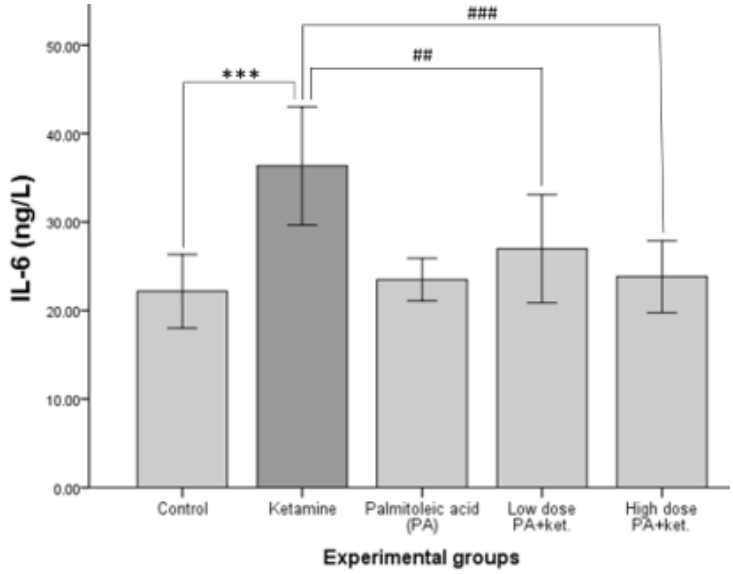

Figure 3. *The serum levels of IL-6 across the experimental groups. Data are shown as Mean ± SD (n=9 in each group). Ketamine administration raised serum levels of IL-6 significantly, while palmitoleic acid pretreatment decreased this increase markedly at both tested doses. ***p < 0.001 versus control group; ##p < 0.01 and ###p < 0.001 versus ketamine group.*

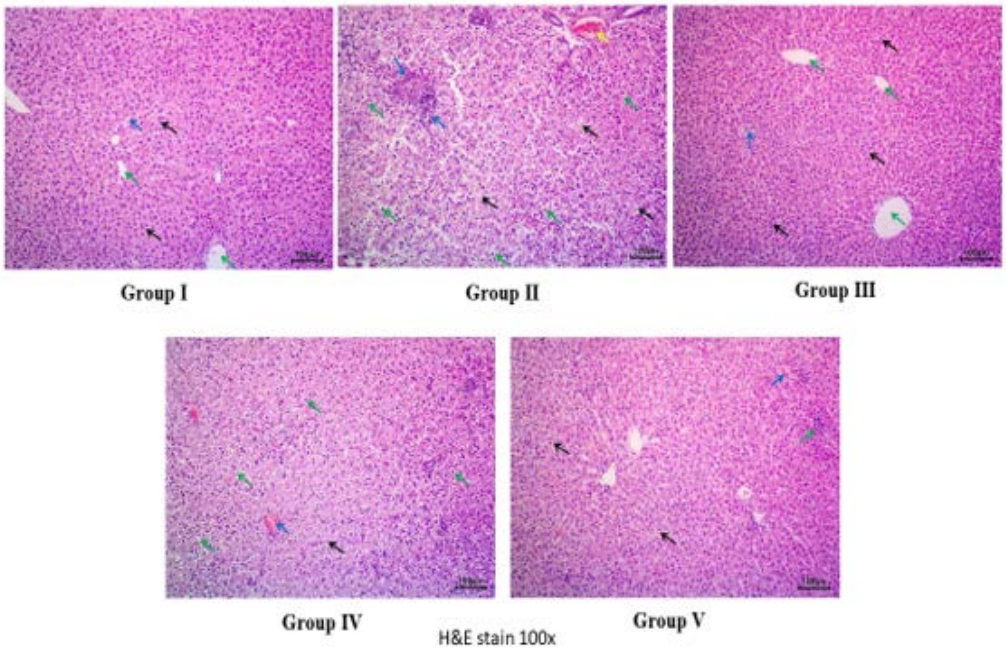

Figure 4. *Hepatoprotective effects of low dose palmitoleic acid against ketamine insult. Group I (control), Group II (160mg.kg^{-1}), Group III (palmitoleic acid-only), Group IV (palmitoleic acid 100mg.kg^{-1+} ketamine), and group V (palmitoleic acid 300mg.kg^{-1+} ketamine). H & E(100x) sections of Group I show intact hepatocytes with organized structure and normal liver architecture, ketamine-group (Group II) shows oncotic necrosis (black arrow), diffuse hydropic degeneration of the hepatocytes (green arrow), severe infiltration of the inflammatory cells in the portal area (black arrow) and congestion of the portal vein (yellow arrow). The Group III shows intact hepatocytes with organized structure (black arrow), central vein (green arrow), and portal area (blue arrow). Group IV; Palmitoleic acid, omega-7, 100mg/kg, shows mild oncotic necrosis (black arrow), diffuse hydropic degeneration of the hepatocytes (green arrow), and congestion of the central vein (blue arrow). Histological section of rat liver from Group V (palmitoleic acid, 300mg/kg) shows very mild hydropic degeneration of the hepatocytes (black arrow), very mild infiltration of the inflammatory cells in the portal area (green arrow), and congestion of the portal vein (blue arrow). Hematoxylin and eosin stained (H&E), Scale bar, 100µm.*

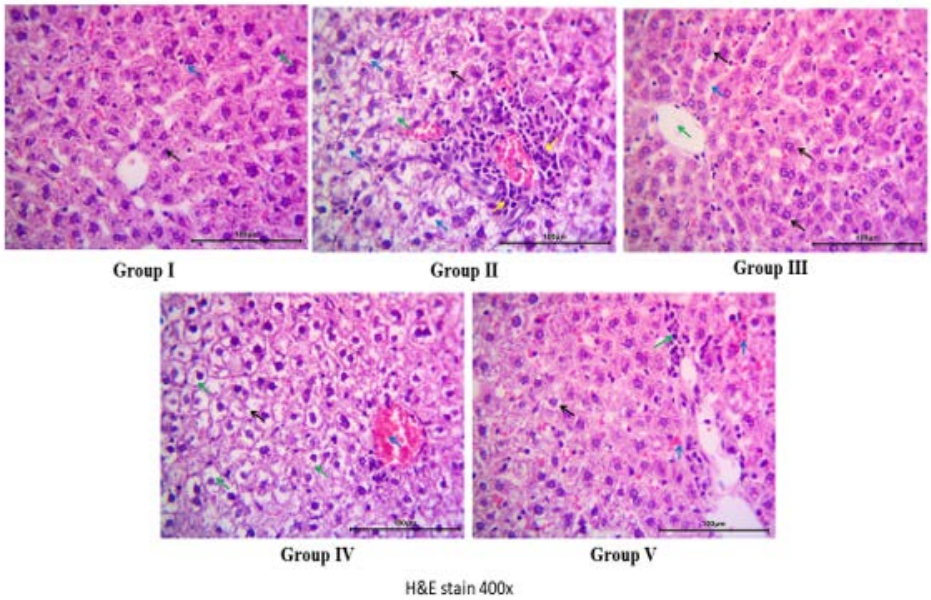

Figure 5. *Hepatoprotective effects of high dose palmitoleic acid against ketamine insult. Group I (control), Group II (160mg.kg^{-1}), Group III (palmitoleic acid-only), Group IV (palmitoleic acid 100mg·kg^{-1}+ ketamine), and group V (palmitoleic acid 300 mg·kg^{-1}+ ketamine). H & E(400x) sections of Group I show normal morphology of hepatocyte with intact nuclei and cell borders. Group II (ketamine-treated) shows marked oncotic necrosis, hydropic degeneration of hepatocytes, severe inflammatory cell infiltration, and sinusoidal congestion; Group III (palmitoleic acid–only) shows normal hepatocyte morphology without pathological alterations; Group IV (palmitoleic acid, 100 mg/kg/day + ketamine) shows mild hepatocellular degeneration with reduced inflammatory infiltration; Group V (palmitoleic acid, 300 mg/kg/day + ketamine) shows preserved hepatocyte morphology with minimal degenerative and inflammatory changes. Hematoxylin and eosin stained (H&E), Scale bar, 100µm.*

Table 1. *Malondialdehyde (MDA) levels among the study groups.*

Groups	**MDA (ng\ml)**
Group I (negative control)	55.92±7.03
Group II Ketamine(160mg/kg/day) (positive control)	76.67±10.22
Group III Palmitoleic acid only(300mg/kg/day)	56.77±6.48
Group IV Palmitoleic acid(100mg/kg/day) +Ketamine (160mg/kg/day)	62.38±8.20
Group V Palmitoleic acid(300mg/kg/day) +Ketamine (160mg/kg/day)	57.86±6.01

Table 2. *Serum inflammatory cytokine levels (TNF-α and IL-6) among the study groups.*

Groups	**TNF-α (ng/L)**	**IL-6 (ng/L)**
Group I (negative control)	29.05±6.25	22.17±4.16
Group II Ketamine(160mg/kg/day) (positive control)	44.47±6.74	36.33±6.67
Group III Palmitoleic acid only(300mg/kg/day)	30.5±4.5	23.49±2.39
Group IV Palmitoleic acid(100mg/kg/day) +Ketamine (160mg/kg/day)	35.02±7.18	26.97±6.1
Group V Palmitoleic acid(300mg/kg/day) +Ketamine (160mg/kg/day)	31.89±3.29	23.82±4.06

Histopathological findings.

Both Groups I & III showed normal hepatic histological findings characterized by intact hepatocytes, normal architecture, normal portal region & central veins, and intact hepatic sinusoids. The normal findings of liver sections in Group III indicate the safety & tolerability of high-dose palmitoleic acid. While the rats from Group II, which received two intraperitoneal injections of ketamine at a dose of 160 mg/kg/day, showed hepatic necrosis and inflammation. Histopathological findings were seen in this group, including hepatocyte degeneration, infiltration of inflammatory cells, especially within the portal area, oncotic and coagulative necrosis, and hepatic sinusoids & portal vein congestions. Compared with the ketamine-treated group, partial hepatoprotective effects were seen when rats were pretreated with a low dose of palmitoleic acid (100 mg /kg/day) in Group IV. The findings in this group were evidenced by mild oncotic necrosis, mild hydropic degeneration, and decreased infiltration of inflammatory cells. Regarding Group V, nearly full hepatoprotective effects were seen when rats received a high dose of palmitoleic acid prior to ketamine injections. The histopathological findings from Group V showed significant histological improvement demonstrated by preserved hepatic architecture, very mild hydropic degeneration of the hepatocytes, and very mild infiltration of the inflammatory cells in the portal area. These findings indicate strong protective effects of palmitoleic acid at high doses. Histopathological findings are presented in Figures 4 and 5.

Discussion.

Prolonged or high-dose exposure to ketamine is associated with hepatotoxicity and is increasingly recognized as a clinically relevant form of DILI (Drug-Induced Liver Injury) [1]. Idiosyncratic drug-induced liver injury is an unpredictable and difficult condition due to lack of specific biomarkers to confirm diagnosis. Therefore, early recognition and clinical evaluation are important, and following established clinical guidelines can help patient management and reduce the risk of developing severe liver injury [16]. Causality assessment tools such as RUCAM are commonly used to support DILI attribution [17]. Recent clinical investigations have demonstrated that long-term ketamine infusion is independently associated with cholestatic liver injury and progressive cholangiopathy in critically ill patients [8]. Reports of secondary sclerosing cholangitis associated with ketamine further support the idea that long-term exposure could damage the liver and gallbladder [18]. Notably, there appears to be a dose-response association between the administration of ketamine and the improvement of clinical outcomes and reduction of cholestatic damage in burn patients [9]. Similarly, case studies in recreational users of ketamine have shown biliary system anomalies and severe cholestasis after long-term usage [19].

From a molecular perspective, ketamine undergoes significant metabolism in the liver mostly via CYP450 isoenzymes, yielding active metabolites such as norketamine, which may contribute to systemic toxicity [20]. The load of hepatic biotransformation, together with the generation of oxidative stress and activation of inflammation, may help explain why some people are more likely to develop liver damage [7,20].

Oxidative stress and inflammation play important roles in ketamine-induced liver damage. As shown in this study, ketamine caused liver injury, which is reflected by higher levels of inflammatory cytokines (IL-6, TNF-α), malondialdehyde (MDA), and histopathological alterations. Among these, oxidative stress is recognized as a major contributor to drug-induced liver injury because it can lead to mitochondrial dysfunction, enhance peroxidation of lipid, decrease ATP production, and then lead to hepatocyte necrosis [3,21]. Lipid peroxidation, reflected by increased MDA, represents a hallmark of reactive oxygen species-mediated membrane injury and may trigger ferroptosis-related pathways in hepatic tissue [22,23]. Transcription of pro-inflammatory cytokines (TNF-α, IL-6) is promoted in the presence of a high level of reactive oxygen species (ROS) that can activate NF-κB signaling, as the sequence amplifies hepatocellular injury [21,24]. Experimental models have confirmed that ketamine administration increases oxidative and inflammatory markers in rat liver tissue [10]. The histopathological findings observed in the ketamine-treated group (Group II) such as oncotic necrosis, hydropic degeneration, inflammatory infiltration, and sinusoidal congestion, are consistent with oxidative stress-driven necroinflammatory injury patterns described in experimental hepatotoxicity models [3].

A clear dose-dependent hepatoprotective effect of palmitoleic acid is a principle finding of this study. Pretreating rats with palmitoleic acid significantly attenuated lipid peroxidation and inflammatory cytokine elevation, with the higher dose (300 mg/kg/day) restoring biochemical and histological parameters toward near-normal values. Establishing how the effects change with different doses enhances the result's biological credibility and supports possible translations into clinical practice [1].

Palmitoleic acid (cis-16:1 n-7), omega-7, is increasingly characterized as a bioactive lipokine with immunometabolic regulatory functions rather than merely a structural fatty acid [25,26]. Palmitoleate suppresses pro-inflammatory macrophage polarization and reduces cytokine production through AMPK-dependent signaling pathways as demonstrated in mechanistic investigations [27]. Additionally, palmitoleic acid suppresses hepatic inflammation and promotes anti-inflammatory myeloid cell phenotypes, supporting its hepatoprotective role as shown in a high-fat diet model [13].

Palmitoleic acid attenuates systemic inflammation and modulates inflammasome activation as seen in recent evidence consistence with our findings that significant reductions are observed in serum levels of TNF- α and IL-6 in palmitoleic acid-pretreated groups [12]. Moreover, emerging data suggest that palmitoleate regulates lipid metabolism and ferroptosis-associated pathways, thereby limiting oxidative hepatocellular damage [15]. Additional studies demonstrate improved hepatotoxic outcomes following palmitoleic acid administration in metabolic and stress-induced liver injury models [14]. The attenuation of MDA in our study is therefore biologically coherent with suppression of lipid peroxidation and restoration of redox homeostasis [28].

Histologically, the normal liver structure is largely preserved with high-dose palmitoleic acid. The agreement between oxidative stress markers, inflammatory cytokines and hepatic architecture strengthens the reliability of the findings and promotes the idea that modulation of oxidative-inflammatory pathways plays a key role in the protection mechanism. Future investigations incorporating Nrf2-regulated antioxidant responses, mitochondrial bioenergetics assessment, and macrophage polarization markers would further delineate upstream signaling pathways and enhance mechanistic resolution [29,30].

The findings of this study together provided evidence that palmitoleic acid mitigated the ketamine-induced hepatotoxicity in dose-responsiveness way through the reduction of inflammatory signals and oxidative stress. Using standard body surface area normalization (the Reagan-Shaw conversion factor of 6.2 for rats to humans), the rat doses of 100 mg/kg and 300 mg/kg correspond to approximate human equivalent doses of 16.1 mg/kg and 48.4 mg/kg, respectively. For a 70 kg adult, these would be roughly 1127 mg and 3388 mg per day. Given that a typical commercial palmitoleic acid supplement (e.g., Provinal®) contains approximately 210 mg per capsule, the human equivalent of our lowest rat dose is about 5–6 capsules daily, and our highest dose equates to roughly 16 capsules per day. While these amounts exceed typical supplement intake levels, prior clinical studies have reported that palmitoleic acid is generally well-tolerated at doses up to 4.5 g per day (4500 mg), with no significant adverse effects or overdose risks aside from mild gastrointestinal discomfort [31,32]. Furthermore, toxicological data indicate a high safety margin, with no observed adverse effect levels in rodent studies far exceeding our administered doses. Therefore, although our doses are supraphysiological relative to standard supplementation, they remain within or near the range previously tested in humans for short-term use [33,34]. This contextualization underscores that our findings have translational relevance, particularly for scenarios involving elevated oxidative stress and inflammation, while also acknowledging that dose extrapolation to humans requires caution and further clinical validation.

Conclusion.

Significant hepatic damage is produced following ketamine administration which led to marked oxidative stress, increase in inflammatory cytokines and marked histopathological lesions in rat livers. The pretreatment with palmitoleic acid demonstrated hepatoprotective effects, evidenced by a reduction in oxidative stress, as revealed by decreased serum MDA levels, diminished systemic inflammation (lower TNF-α and IL-6), and enhanced histological architecture. The greatest consistent benefit came from the largest dose of palmitoleic acid.

REFERENCES

1. Allison R, Guraka A, Shawa IT, et al. Drug induced liver injury – a 2023 update. Journal of Toxicology and Environmental Health, Part B. 2023;26:442-467.
2. Fontana RJ, Liou I, Adrian R, et al. AASLD practice guidance on drug, herbal, and dietary supplement–induced liver injury. Hepatology. 2023;77:1036-1065.
3. Villanueva-Paz M, Morán L, López-Alcántara N, et al. Oxidative Stress in Drug-Induced Liver Injury (DILI): From Mechanisms to Biomarkers for Use in Clinical Practice. Antioxidants. 2021;10:390.
4. Cichoż-Lach H. Oxidative stress as a crucial factor in liver diseases. World J Gastroenterol. 2014;20:8082.
5. Domino EF, Warner DS. Taming the Ketamine Tiger. Anesthesiology. 2010;113:678-684.
6. Li L, Vlisides PE. Ketamine: 50 Years of Modulating the Mind. Front Hum Neurosci. 2016;10.
7. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol Rev. 2018;70:621-660.
8. Wendel-Garcia PD, Erlebach R, Hofmaenner DA, et al. Long-term ketamine infusion-induced cholestatic liver injury in COVID-19-associated acute respiratory distress syndrome. Crit Care. 2022;26:148.
9. De Tymowski C, Dépret F, Dudoignon E, et al. Ketamine restriction correlates with reduced cholestatic liver injury and improved outcomes in critically ill patients with burn injury. JHEP Reports. 2024;6:100950.
10. Bedir Z, Ozkaloglu Erdem KT, Ates I, et al. Effects of ketamine, thiopental and their combination on the rat liver: A biochemical evaluation. Advances in Clinical and Experimental Medicine. 2021;31:285-292.

11. Bermúdez MA, Meana C, Garrido A, et al. Phosphatidylcholine-bound palmitoleic acid: A bioactive key to unlocking macrophage anti-inflammatory functions. Biomedicine & Pharmacotherapy. 2025;192:118652.
12. Sahoo PK, Ravi A, Liu B, et al. Palmitoleate protects against lipopolysaccharide-induced inflammation and inflammasome activity. J Lipid Res. 2024;65:100672.
13. Souza CO, Teixeira AAS, Biondo LA, 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;1865:158776.
14. Han Q, Liu Y, Liu X, et al. Palmitoleic Acid Inhibits Hepatotoxic Effects by Reducing Trimethylamine-N-Oxide (TMAO) Formation in High L-Carnitine-Treated Mice. Nutrients. 2024;16:3599.
15. Wang H, Shan C, Guo G, et al. Therapeutic potential of palmitoleic acid in non-alcoholic fatty liver disease: Targeting ferroptosis and lipid metabolism disorders. Int Immunopharmacol. 2024;142:113025.
16. Andrade RJ, Aithal GP. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70:1222-1261.
17. Danan G, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. International Journal of Molecular Sciences. 2016;17:14.
18. Mallet V, Bock K. Intravenous ketamine and progressive cholangiopathy in COVID-19 patients. J Hepatol. 2021;74:1243-4.
19. Garkusha LK, Lin Z, Lee A. A case series of recreational ketamine-induced cholangiopathy. Annals of Internal Medicine: Clinical Cases. 2024;3:e230993.
20. Dinis-Oliveira RJ. Metabolism and metabolomics of ketamine: a toxicological approach. Forensic Sci Res. 2017;2:2-10.
21. Sies H. Oxidative Stress: Concept and Some Practical Aspects. Antioxidants. 2020;9:852.
22. Jaeschke H, Ramachandran A. Ferroptosis and Intrinsic Drug-induced Liver Injury by Acetaminophen and Other Drugs: A Critical Evaluation and Historical Perspective. J Clin Transl Hepatol. 2024;12:1057-1066.
23. Ayala A, Muñoz MF, Argüelles S. Lipid Peroxidation: Production, Metabolism, and Signaling Mechanisms of Malondialdehyde and 4-Hydroxy-2-Nonenal. Oxid Med Cell Longev. 2014;2014:1-31.
24. Lawrence T. The Nuclear Factor NF- B Pathway in Inflammation. Cold Spring Harb Perspect Biol. 2009;1:a001651-a001651.
25. Bermúdez MA, Pereira L, Fraile C, et al. Roles of Palmitoleic Acid and Its Positional Isomers, Hypogeic and Sapienic Acids, in Inflammation, Metabolic Diseases and Cancer. Cells. 2022;11:2146.
26. Cao H, Gerhold K, Mayers JR, et al. Identification of a Lipokine, a Lipid Hormone Linking Adipose Tissue to Systemic Metabolism. Cell. 2008;134:933-944.
27. Chan KL, Pillon NJ, Sivaloganathan DM, et al. Palmitoleate Reverses High Fat-induced Proinflammatory Macrophage Polarization via AMP-activated Protein Kinase (AMPK). Journal of Biological Chemistry. 2015;290:16979-88.
28. Del Rio D, Stewart AJ, Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutrition, Metabolism and Cardiovascular Diseases. 2005;15:316-28.
29. Zhou J, Zheng Q, Chen Z. The Nrf2 Pathway in Liver Diseases. Front Cell Dev Biol. 2022;10.
30. Ma Q. Role of Nrf2 in Oxidative Stress and Toxicity. Annu Rev Pharmacol Toxicol. 2013;53:401-426.
31. Tamargo J, Tamargo M. Pharmacokinetics and safety profile of omega-3 polyunsaturated fatty acids. Omega-3 Fatty Acids: Keys to Nutritional Health. 2016:541-84.
32. Hasan M. Hasan, Zeina A. Al-Thanoon, Marwan M. Merkhan. Therapeutic potential of omega-7 in mitigating doxorubicin-induced hepatotoxicity in albino rats. 2MEDICINSKI ČASOPIS. 2026;60:1-10.
33. Fadhel M, Faris Hassan A. Anti-inflammatory effect of omega-7 against doxorubicin-induced cardiotoxicity in male rats: An observational study. F1000Research. 2023;12:36.
34. Fadhel M, Ali F Hassan. Protective Effect of Omega-7 against Doxorubicin-Induced Cardiotoxicity in Male Rats. IJPS. 2023;32:35-40.