Journal of Medical and oral biosciences
ISSN (Online): 3007-9551
ISSN (Print): 3007-9543

JMOB
Open Access DOAJ

IRAQI Academic Scientific Journals

Type: Research article
Publish online: 30/ 05 /2026

Ameliorative effect of Rosuvastatin on Hepatic Tissue in Rat Model Exposed to Methotrexate

Zahraa Younus saeed [1*]

[1] Department of biology, College of education for pure sciences, University of Al-Hamdaniya, Iraq
Email: Pharmacistzahra89@uohamdaniya.edu.iq
ORCID: https://orcid.org/ 0009-0008-9262-8036

OPEN ACCESS

ARTICLE INFO

Received: 02 /05/2026
Revised: 18/ 05/ 2026
Accepted: 23 / 05 / 2026
Publish online: 30 / 05 / 2026
Plagiarism percentage at publication: 14%

*** Corresponding Author:** Zahraa Younus saeed
Email: Pharmacistzahra89@uohamdaniya.edu.iq

CITATION

Zahraa Younus saeed. (2026). Ameliorative effect of Rosuvastatin on Hepatic Tissue in Rat Model Exposed to Methotrexate. JMOB. 3; (2): 166-176. https://doi.org/10.58564/jmob.177

COPYRIGHT

© Zahraa Younus saeed. (2026). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY-SA 4.0). The use, distribution or reproduction in other forums is allowed, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Abstract

The research aims to examine the therapeutic effect of rosuvastatin (RSV) on methotrexate (MTX)- induced liver toxicity, focusing on tissue integrity and oxidative damage. For this aim, 30 adult albino-type male rats were categorized into 3 groups of 10 rats each: normal control, MTX-treated, and MTX+RSV-treated. Intraperitoneal administration of 20 mg/kg MTX was utilised to induce liver toxicity in MTX-treated and MTX+ RSV -treated groups on day 1. Following induction, MTX+ RSV -treated rats were orally delivered RCV at 20 mg/kg as a therapeutic intervention for one week. The therapeutic duration was contingent upon prior research. Histopathological and biochemical parameters, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were assessed, along with the expression of oxidative stress indicators (malondialdehyde (MDA) and reduced glutathione (GSH)) in hepatic tissue. Results revealed that RSV markedly reduced the severity of MTX-induced hepatic injury by attenuating elevations in hepatic biochemical markers, including ALT and AST, and simultaneously rectifying histological abnormalities. Moreover, RSV therapy in MTX-exposed rats markedly decreased oxidative stress markers, including MDA, while increasing the level of antioxidative molecules, notably GSH, in hepatic tissues. The study concluded that RSV may help against MTX-provoked hepatic injury, due to its robust antioxidant and anti-inflammatory properties.

Keywords: Methotrexate, hepatic injury, rosuvastatin.

Introduction

Drug-induced hepatotoxicity results in the withdrawal of several clinically approved drugs due to their harmful side effects (1). The liver metabolizes the majority of drugs, and factors such as alcohol use, malnutrition, infection, and anemia that compromise liver function may lead to hepatotoxicity after drug delivery (2).
Methotrexate (MTX) has anticancer, anti-inflammatory, and immunosuppressive properties. Nevertheless, it may potentially pose risks and impact several organs (3). MTX inhibits the synthesis of DNA and RNA by blocking the function of the enzyme dihydrofolate reductase (4). It also inhibits cells from entering mitosis, hence decelerating cell growth. Another harmful mechanism of MTX is its promotion of apoptosis in reaction to oxidative stress (5).

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

RSV is a medication used to manage elevated amounts of detrimental lipids and cholesterol in the bloodstream. It functions by blocking the enzyme HMG-CoA reductase inside the mevalonate pathway (6-8). This inhibition impedes isoprenylation, which is crucial for modulating cell proliferation, stimulating the pro-inflammatory cytokines production, and generating reactive oxygen species (ROS) (9). A recent paper has emphasized the advantages of using this medication to preserve liver function. Prior studies have shown that RSV may successfully avert liver injury caused by fipronil in male rats by mitigating oxidative damage and indicators of apoptosis (10). The therapeutic effects of RSV on inflammatory and oxidative damage have been recorded in many inflammatory illnesses (11, 12). Nevertheless, there is inadequate evidence about the effectiveness of RSV in MTX-induced hepatic tissue toxicity. This research examined the ameliorative effect of RSV on MTX-provoked hepatic injury in male Wistar albino rats by analyzing biochemical, histological, and oxidative damage indicators.

Materials and Methods

Rats were accommodated in individual, sanitized polypropylene cages devoid of contaminants. The cages feature a robust wire-mesh structure that is maintained in a hygienic condition, thereby preventing the rats from licking or contacting one another. The structure had a ventilation system that perpetually circulated air, along with access to potable water and consistently accessible food. Before commencing the experiment, animals were let a week to acclimatize to their new environment.

Ethical approval

The research was conducted in accordance with the ethical standards for health studies established by the Research Ethics Committee of Al-Hamdaniya University, Al-Hamdaniya, Iraq.(Approval No. UH.2026.005).

Experimental Design

Rats were allocated into 3 groups, with 10 rats per group. Group I received normal saline and functioned as the vehicle control, while liver toxicity was evoked in Group II by intraperitoneal injection of 20 mg/kg MTX. Group II administered oral normal saline, lastly, group III treated orally with RCV at a dose of 20 mg/kg orally post-induction of hepatotoxicity for 7 days. The treatment duration was contingent upon prior investigations of experimental hepatotoxicity. The blood was taken via heart puncture with a 5ml syringe, conveyed to a gel tube, then incubated at 37 °C for 30 minutes before being centrifuged at 4000 for 10 minutes. The serum was stored at -20 °C for biochemical and histological experiments. The rats were dissected, and the hepatic tissue was preserved in 10% formaldehyde for assay analysis.

Chemicals and drugs

RCV was obtained from AstraZeneca, UK, while MTX was sourced from Koçak Farma (Turkey). Estimated pharmaceutical was formulated as suspensions in purified

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

water. RCV was administered at a dose of 20 mg/kg as a therapeutic intervention in rats, based on research indicating its maximum inhibitory effect on oxidative and inflammatory modulation (13).

Evaluation of liver function indicators in serum

An automated analyzer (ARCHITECT c4000 Chemistry Analyzer, Abbott Diagnostics, USA) and appropriate kits (ALT2 and AST2) provided by Abbott Diagnostics were prepared to assess liver function parameters (ALT and AST) in serum, following the guidelines of manufacturer.

Measurements of oxidative stress biomarkers

The MDA and GSH levels were assessed in the rat hepatic tissues that were obtained by using standardized enzyme-linked immunosorbent assay kits following the instruction of manufacturer. “The hepatic tissues were swiftly removed, rinsed, hydrated, and examined following irrigation with cold phosphate-buffered saline. Tissue samples were homogenized with a transparent blender and subsequently centrifuged at 10,000 × g for 15 minutes at 4°C. After collection, the residual material was utilized in biochemical experiments. A colorimetric assay utilising the thiobarbituric acid-reactive substances method was employed to quantify MDA, an indicator of lipid peroxidation. The results were quantified as nmol MDA/mg protein, with absorbance assessed at 532 nm. GSH levels were measured using a colorimetric technique that relies on the reaction with 5,5′-dithiobis. The absorbance was determined at 405 nm, and the outcomes were reported as µmol GSH per mg of protein”.

Histological assessments

Following extraction, “hepatic tissue specimens from rats were immediately fixed in 10% buffered formalin, dehydrated with graded ethanol, and cleaned with xylene. The sample was then submerged in paraffin and put on chilled plates to form paraffin blocks. The hepatic specimens were subsequently sliced into 4- to 5-µm sections utilizing a microtome. A water soak was employed to deposit the slide portion, and several milliliters of di-n-butyl phthalate in xylene were introduced to the tissue fragment before the coverslip was applied. An optical microscope was employed for conducting blind tests and evaluations.

Statistical Analysis

The data underwent statistical examination using suitable analytical methodologies. Descriptive statistics were presented as mean values along with their standard deviations. Differences among groups were determined by one-way analysis of variance, and Tukey's post hoc test for multiple comparisons. Statistical significance was considered at a P-value of less than 0.05.

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

Results

Effect of tested agents on liver function, and oxidative stress biomarkers

The MTX group had markedly higher ALT and AST levels than the control group. The MTX+ RSV group had considerably lower levels of these two enzymes compared with the MTX group ($p < 0.05$) (Figure. 1).

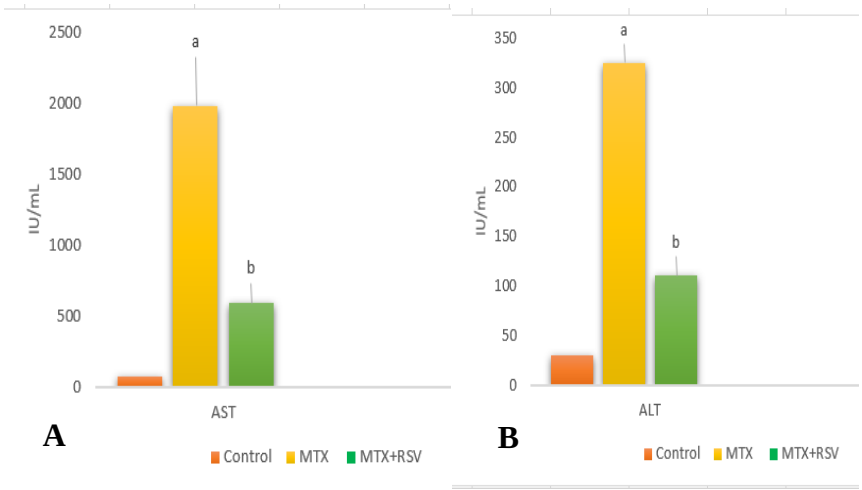

Figure. 1: Shows the effects of tested agents on liver enzymes AST (A) and ALT (B) levels in methotrexate-induced liver toxicity. The data are shown as Mean ± SD; (a): Substantial from the normal control; (b): Substantial from the methotrexate group. MTX: Methotrexate, RSV: Rosuvastatin, AST: aspartate transaminase, and ALT: alanine transaminase

Compared with the control group, the MTX group had substantially higher levels of MDA. The MTX+ RSV group had markedly reduced levels of the MDA compared to the MTX group ($p < 0.05$) (Figure. 2).

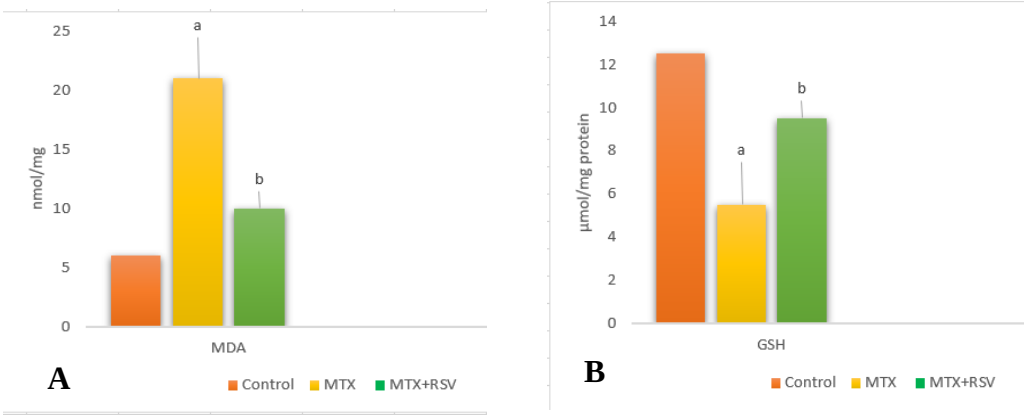

Figure 2: Effects of tested agents on oxidative (A): MDA, and anti-oxidative stress markers (B): GSH. The data are shown as Mean ± SD; (a): Substantial from the normal control; (b): Substantial from the methotrexate group. MTX: Methotrexate, RSV: Rosuvastatin , MDA: Malondialdehyde, GSH: Glutathione

The Journal of medical and Oral Biosciences

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

The antioxidative marker GSH was significantly reduced in the MTX group compared with the control group. However, the MTX+ RSV groups exhibited notably higher GSH levels relative to the induction group ($p < 0.05$).

Effects of tested agents on histopathological evaluation

Figures. 3 (A and B) demonstrate that the histopathological analysis of liver specimens from the control group had intact histological architecture, characterized by hepatocytes (black arrow), central vein (green arrow), and sinusoids containing Kupffer cells (blue arrow).While, Figure. 4 (A and B) illustrates that liver samples from the untreated induction group had extensive lesions characterized by hepatocytic necrosis (black arrow), cellular edema (green arrow), sinusoidal enlargement (blue arrow), and congestion (red arrow). Nonetheless, as seen in 5 (A, B), the histological examination of the MTX+ RSV group revealed minor lesions characterized by single hepatocyte necrosis (black arrow), preserved sinusoids (green arrow), and central venous congestion (blue arrow).

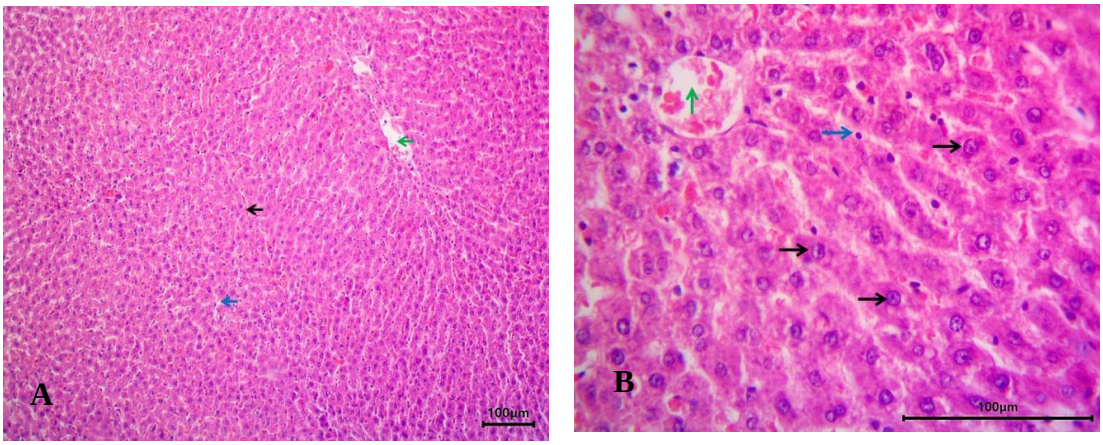

Figure. 3: Effects of tested agents on histopathology changes the liver tissue of the control group (H&E 100X, 400X).

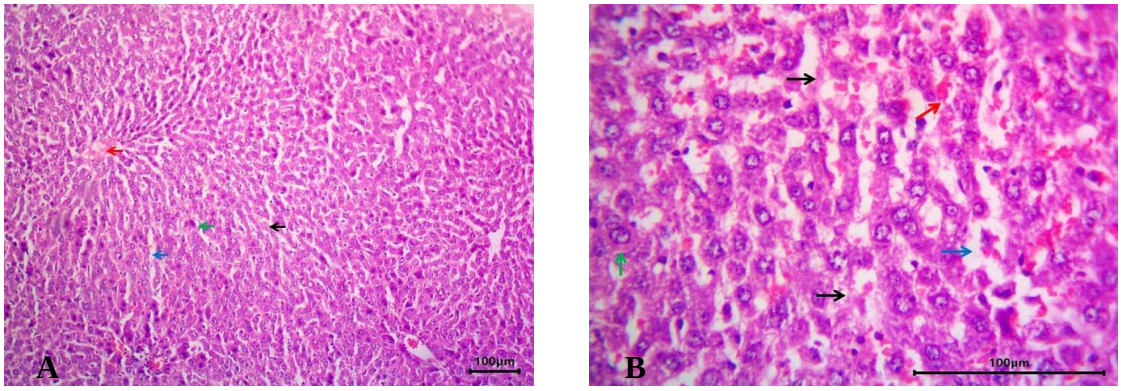

Figure.4: Impact of tested agents on histopathology changes the liver tissue of the MTX group (H&E 100X, 400X).

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

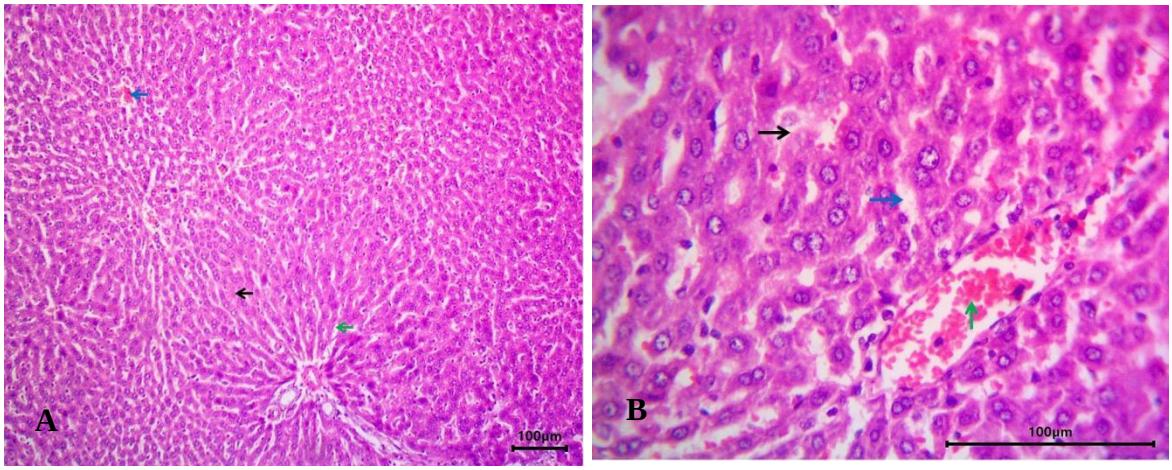

Figure. 5: Impact of tested agents on histopathology changes of the liver tissue of the MTX+ RSV group (H&E 100X, 400X)

Discussion

This research conducted a series of tests to examine the fundamental mechanisms of RSV 's therapeutic effects on hepatic tissues. The outcomes demonstrated a significant rise in liver biochemical markers (ALT and AST) after MTX treatment versus the control group. ALT and AST are the most reliable liver necrosis indicators (14). An elevation in their activity in the serum indicates a compromise of the cell membrane, correlated with hepatocyte apoptosis (15). Liver damage has been reported, particularly with acute high doses or extended use of MTX (16, 17). Elevated concentrations of the polyglutamated form enhance the drug's intracellular retention, which has been suggested as an explanation for MTX-induced liver toxicity (18, 19). This findings compatible with established hepatotoxic effects of MTX use, characterized by oxidative stress, upregulation of inflammatory markers, and resultant hepatic cellular injury. This damage leads to the release of enzymes into the circulation, signifying hepatotoxicity (20). The significant elevation in ALT and AST levels signifies hepatic injury. Furthermore, the research findings demonstrated that MTX treatment resulted in higher MDA levels and lower GSH antioxidant enzyme activity in liver tissue. Oxidative stress occurs due to an imbalance between ROS and antioxidant defenses, eventually impairing the cell's enzymatic and non-enzymatic functions (21). Reduced glutathione is an essential element of the intrinsic antioxidant defense mechanism against oxidative injury, while malondialdehyde is an established indicator of lipid peroxidation (22). These results corroborate previous studies, demonstrating increased malondialdehyde levels and reduced glutathione content after MTX toxicity in the hepatic tissues of a rat model (23-28). Oxidative stress is regarded as an essential determinant in hepatic tissue damage caused by MTX (29). Oxidative stress caused by MTX treatment in liver tissue was mitigated by the administration of RSV for 7 days, indicating the drug's antioxidant properties. Experimental research has shown that free radicals resulting from oxidative stress are the principal mechanism behind induced hepatotoxicity (30, 31). Oxidative stress, caused by free radicals, is a critical marker of hepatic impairment. The oxidation

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

of cyclophosphamide produces ROS and lipid peroxidation (LPO) during inflammation, resulting in hepatic cell injury, disruption of the redox cycle, and elevated LPO levels (32). Elevating LPO levels in experimental rats using MDA as the primary oxidized byproduct (33). Maheshwari et al. 2015 (34) demonstrated that RSV significantly reduced oxidative stress by enhancing glutathione levels and lowering MDA levels in colitis models. Additionally, another study (35) confirmed that RSV significantly lower oxidative stress by decreasing MDA levels in rats. Histopathological examination validated biochemical alterations, implying significant hepatic injury in the MTX-treated animals. In contrast, the RSV -treated group displayed notable damage, suggesting that RSV may have a partial hepato-protective effect. The administration of RSV significantly reduced biochemical and histological changes, suggesting its potential to alleviate MTX-induced hepatocellular injury. The theory asserts that the accumulation of MTX polyglutamates within the cell leads to folate deficiency, oxidative damage, the production of pro-inflammatory indicators, and genetic diversity (36, 37). The gut microbiota is expected to be the principal driver of hepatocellular carcinoma and hepatic fibrosis development (38-41).

Conclusion

Rosuvastatin markedly relieves these detrimental effects, demonstrating its efficacy as a robust antioxidant and anti-inflammatory drug. Rosuvastatin alleviates the adverse effects of methotrexate by augmenting cellular protection and improving the well-being of rats. These findings will offer substantial prospective into the possible therapeutic application of rosuvastatin for drug-induced hepatic injury.

Declarations

Acknowledgment
The author sincerely acknowledge the College of Education for Pure Sciences at the University of Al-Hamdaniya for its resources and unwavering support.

Competing interests statement
There is no conflict of interest to declare.

Ethics statement
The research was conducted in accordance with the ethical standards for health studies established by the Research Ethics Committee of Al-Hamdaniya University, Al-Hamdaniya, Iraq.(Approval No. UH.2026.005).

Funding
This research not received fund

Author contributions

ZYS designed the study conception and did the data analysis, interpretation of results, manuscript writing, revision, and approved of the final manuscript publication.

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

References

1. Babai S, Auclert L, Le-Louët H. Safety data and withdrawal of hepatotoxic drugs. Therapie. 2021 Nov-Dec;76(6):715-723. doi: 10.1016/j.therap.2018.02.004. Epub 2018 Feb 21. PMID: 29609830.

2. Björnsson H, Björnsson E. Drug-induced liver injury: Pathogenesis, epidemiology, clinical features, and practical management. Eur J Intern Med. 2022;97:26-31. doi: 10.1016/j.ejim.2021.10.035. Epub 2021 Nov 9. PMID: 34772600

3. Saravanan V, Kelly C. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. Rheumatology. 2004;43(2):143-7. doi: 10.1093/rheumatology/keg466. Epub 2003 Aug 15. PMID: 12923285

4. Al-Refai A, Ali A, Kamal K. Immunohistochemical study of the effect of green tea extract on methotrexate-induced oral mucositis in albino rats. J Cytol Histol. 2014;5(3):1-7. doi.org/10.4172/2157-7099.1000227

5. Ezhilarasan D. Hepatotoxic potentials of methotrexate: Understanding the possible toxicological molecular mechanisms. Toxicology. Doi: 2021;458:152840. 10.1016/j.tox.2021.152840. Epub 2021 Jun 24. PMID: 34175381.

6. Oda H, Keane WF. Recent advances in statins and the kidney. Kidney Int. 1999;56:S2-S5. doi: 10.1046/j.1523-1755.1999.07101.x. PMID: 10412725

7. Aljawad FH, Hashim HM, Jasim GA, Kadhim HM, Gorgi AQ, Jawad RF. Effects of atorvastatin and coenzyme Q10 on glycemic control and lipid profile in type 2 diabetic patients. Int J Pharm Sci Rev Res. 2015;34(2):183-6.

8. ATTARBASHEE RK. The antitoxic effect of the rosuvastatin in the cyclophosphamide-induced liver toxicity in male rats. Assiut Veterinary Medical Journal. 2025;71(185):187-203.

9. Abdel-Daim MM, Abdeen A. Protective effects of rosuvastatin and vitamin E against fipronil-mediated oxidative damage and apoptosis in rat liver and kidney. Food Chem Toxicol. 2018;114:69-77. doi: 10.1016/j.fct.2018.01.055. Epub 2018 Feb 9. PMID: 29432839

10. Arulpriya P, Lalitha P, Hemalatha S. Antimicrobial testing of the extracts of Samanea saman (Jacq.) Merr. 2010.

11. Yamagata T, Kinoshita K, Nozaki Y, Sugiyama M, Ikoma S, Funauchi M. Effects of pravastatin in murine collagen-induced arthritis. Rheumatol Int. 2007;27(7):631-9. doi: 10.1007/s00296-006-0270-9. Epub 2006 Nov 21. PMID: 17119970

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

12. Hamzeh M, Hosseinimehr SJ, Khalatbary AR, Mohammadi HR, Dashti A, Amiri FT. Atorvastatin mitigates cyclophosphamide-induced hepatotoxicity via suppression of oxidative stress and apoptosis in rat model. Res Pharm Sci. 2018;13(5):440-9. doi: 10.4103/1735-5362.236837. PMID: 30271446

13. Attarbashee R. The antitoxic effect of the rosuvastatin in the cyclophosphamide-induced liver toxicity in male rats. Assiut Vet Med J 71: 187–203. 2025.

14. Center SA. Interpretation of liver enzymes. Vet Clin North Am Small Anim Pract. 2007;37(2):297-333. doi: 10.1016/j.cvsm.2006.11.009. PMID: 17336677.

15. McGill MR. The past and present of serum aminotransferases and the future of liver injury biomarkers. EXCLI journal. 2016;15:817. doi: 10.17179/excli2016-800. eCollection 2016. PMID: 28337112 PMCID: PMC5318690

16. Şener G, Ekşioğlu-Demiralp E, Cetiner M, Ercan F, Şirvancı S, Gedik N, et al. L-Carnitine ameliorates methotrexate-induced oxidative organ injury and inhibits leukocyte death. Cell Biol Toxicol. 2006;22(1):47-60. doi: 10.1007/s10565-006-0025-0. PMID: 16463019

17. Uraz S, Tahan V, Aygun C, Eren F, Unluguzel G, Yuksel M, et al. Role of ursodeoxycholic acid in prevention of methotrexate-induced liver toxicity. Dig Dis Sci. 2008;53(4):1071-7. doi: 10.1007/s10620-007-9949-3. Epub 2007 Oct 13. PMID: 17934844.

18. Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, et al. Methotrexate an old drug with new tricks. Int J Mol Sci. 2019;20(20):5023. doi: 10.3390/ijms20205023. PMID: 31658782 PMCID: PMC6834162

19. Jahovic N, Çevik H, Şehirli AÖ, Yeğen BÇ, Şener G. Melatonin prevents methotrexate-induced hepatorenal oxidative injury in rats. Journal of pineal research. 2003;34(4):282-7. doi.org/10.1034/j.1600-079X.2003.00043.x PMID: 12662351

20. Dalaklioglu S, Genc G, Aksoy N, Akçit F, Gumuslu S. Resveratrol ameliorates methotrexate-induced hepatotoxicity in rats via inhibition of lipid peroxidation. Hum Exp Toxicol. 2013;32(6):662-71. doi: 10.1177/0960327112468178. Epub 2013 Feb 19. PMID: 23424212

21. Ozougwu JC. The role of reactive oxygen species and antioxidants in oxidative stress. International Journal of Research. 2016;1(8):1-8. doi: 10.1155/2016/3164734. PMCID: PMC4736974 PMID: 26881021

22. Ighodaro O, Akinloye O. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria journal of medicine. 2018;54(4):287-93. doi.org/10.1016/j.ajme.2017.09.001

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

23. Tabassum H, Parvez S, Pasha ST, Banerjee BD, Raisuddin S. Protective effect of lipoic acid against methotrexate-induced oxidative stress in liver mitochondria. Food Chem Toxicol. 2010;48(7):1973-9. doi: 10.1016/j.fct.2010.04.047. Epub 2010 May 6. PMID: 20451574.

24. Jahovic N, Şener G, Çevik H, Ersoy Y, Arbak S, Yeğen BÇ. Amelioration of methotrexate-induced enteritis by melatonin in rats. Cell Biochemistry and Function: Cellular biochemistry and its modulation by active agents or disease. 2004;22(3):169-78. doi: 10.1002/cbf.1071. PMID: 15124182.

25. Aithal GP. Hepatotoxicity related to antirheumatic drugs. Nature Reviews Rheumatology. 2011;7(3):139-50. doi: 10.1038/nrrheum.2010.214. Epub 2011 Jan 25. PMID: 21263458

26. Hadi NR, Al-Amran FG, Swadi A. Metformin ameliorates methotrexate-induced hepatotoxicity. Journal of Pharmacology and Pharmacotherapeutics. 2012;3(3):248-53. doi: 10.4103/0976-500X.99426. PMID: 23129960

27. Taysi S, Algburi FS, Taysi ME, Caglayan C. Caffeic acid phenethyl ester: A review on its pharmacological importance, and its association with free radicals, COVID-19, and radiotherapy. Phytother Res. 2023;37(3):1115-35. doi: 10.1002/ptr.7707. Epub 2022 Dec 23. PMID: 36562210

28. Çetin A, Kaynar L, Kocyigit I, Hacioglu SK, Saraymen R, Ozturk A, et al. Role of grape seed extract on methotrexate induced oxidative stress in rat liver. The American journal of Chinese medicine. 2008;36(05):861-72. doi: 10.1142/S0192415X08006302. PMID: 19051353

29. Cetinkaya A, Bulbuloglu E, Kurutas EB, Kantarceken B. N-acetylcysteine ameliorates methotrexate-induced oxidative liver damage in rats. Med Sci Monit. 2006;12(8):BR274-BR8. Epub 2006 Jul 12. PMID: 16865059

30. Chabra A, Shokrzadeh M, Naghshvar F, Salehi F, Ahmadi A. Melatonin ameliorates oxidative stress and reproductive toxicity induced by cyclophosphamide in male mice. Hum Exp Toxicol. 2014;33(2):185-95. doi: 10.1177/0960327113489052. Epub 2013 May 23. PMID: 23703819

31. Winterbourn CC. Are free radicals involved in thiol-based redox signaling? Free Radic Biol Med. 2015;80:164-70. doi: 10.1016/j.freeradbiomed.2014.08.017. Epub 2014 Sep 30. PMID: 25277419

32. Selvakumar E, Prahalathan C, Mythili Y, Varalakshmi P. Mitigation of oxidative stress in cyclophosphamide-challenged hepatic tissue by DL-α-lipoic acid. Mol Cell Biochem. 2005;272(1):179-85. doi: 10.1007/s11010-005-7322-4. PMID: 16010986

33. Haque R, Bin-Hafeez B, Parvez S, Pandey S, Sayeed I, Ali M, et al. Aqueous extract of walnut (Juglans regia L.) protects mice against cyclophosphamideinduced

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/

biochemical toxicity. Hum Exp Toxicol. 2003;22(9):473-80. doi: 10.1191/0960327103ht388oa. PMID: 14580007

34. Maheshwari RA, Balaraman R, Sailor GU, Sen DB. Protective effect of simvastatin and rosuvastatin on trinitrobenzene sulfonic acid-induced colitis in rats. Indian J Pharmacol. 2015;47(1):17-21. doi: 10.4103/0253-7613.150311. PMID: 25821305

35. Qasim S, Alamgeer, Kalsoom S, Shahzad M, Bukhari IA, Vohra F, et al. RETRACTED: Rosuvastatin Attenuates Rheumatoid Arthritis-Associated Manifestations via Modulation of the Pro-and Anti-inflammatory Cytokine Network: A Combination of In Vitro and In Vivo Studies. ACS omega. 2021;6(3):2074-84. doi: 10.1021/acsomega.0c05054. eCollection 2021 Jan 26. PMID: 33521447

36. Fan W-C, Huang C-C, Yang Y-Y, Lin A, Lee K-C, Hsieh Y-C, et al. Serum pentraxin-3 and tumor necrosis factor-like weak inducer of apoptosis (TWEAK) predict severity of infections in acute decompensated cirrhotic patients. Journal of microbiology, immunology and infection. 2017;50(6):905-14. doi: 10.1016/j.jmii.2015.12.006. Epub 2016 Jan 18. PMID: 26872435

37. Şener G, Ekşioğlu-Demiralp E, Çetiner M, Ercan F, Yeğen BÇ. β-glucan ameliorates methotrexate-induced oxidative organ injury via its antioxidant and immunomodulatory effects. Eur J Pharmacol. 2006;542(1-3):170-8. doi: 10.1016/j.ejphar.2006.02.056. Epub 2006 May 17. PMID: 16793036

38. Fox JG, Feng Y, Theve EJ, Raczynski A, Fiala JL, Doernte AL, et al. Gut microbes define liver cancer risk in mice exposed to chemical and viral transgenic hepatocarcinogens. Gut. 2010;59(01):88-97. doi: 10.1136/gut.2009.183749. PMID: 19850960

39. Rogers AB. Distance burning: how gut microbes promote extraintestinal cancers. Gut microbes. 2011;2(1):52-7. doi: 10.4161/gmic.2.1.14761. PMID: 21637019

40. Roderburg C, Luedde T. The role of the gut microbiome in the development and progression of liver cirrhosis and hepatocellular carcinoma. Gut microbes. 2014;5(4):441-5. doi: 10.4161/gmic.29599. Epub 2014 Jul 9. PMID: 25006881

41. Ponziani FR, Bhoori S, Castelli C, Putignani L, Rivoltini L, Del Chierico F, et al. Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. Hepatology. 2019;69(1):107-20. doi: 10.1002/hep.30036. Epub 2018 Jul 10. PMID: 29665135

CC BY-SA 4.0 Attribution-ShareAlike 4.0
https://creativecommons.org/licenses/by-sa/4.0/