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Allium jesdianum Attenuates Oxidative Stress and Inflammatory Responses in the Liver of Cyclophosphamide-Treated Mice

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ABSTRACT

Introduction

The liver is essential for drug metabolism and detoxification, and cyclophosphamide (CTX) can trigger hepatotoxicity via oxidative stress and inflammatory responses. *Allium jesdianum* has antioxidant and anti-inflammatory effects that may mitigate CTX-induced liver injury. This study investigates whether the antioxidant properties of *A. jesdianum* can protect organ function in a CTX-treated animal model, with implications for potential adjunctive strategies in CTX therapy.

Methods and materials

Twenty male NMRI mice divided randomly into 4 groups (n=5 per group): normal saline for 14 days (oral), *A. jesdianum* extract at 200 mg/kg daily for 14 days (oral), CTX at 20 mg/kg intraperitoneal (IP) for 5 days, and *A. jesdianum* extract at 200 mg/kg (oral) daily for 14 days + CTX at 20 mg/kg IP during the last 5 days. Tissue samples were collected and analyzed for lipid peroxidation, antioxidant enzyme activity, and inflammatory cytokines.

Results:

CTX increased thiobarbituric acid reactive substances (TBARS), which were attenuated by *A. jesdianum* ($P < 0.001$). Antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) were adversely modulated by CTX and markedly ameliorated by *A. jesdianum* pretreatment ($p < 0.001$). Pro-inflammatory cytokines (interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) were increased in the CTX group, which was significantly decreased by *A. jesdianum* ($p < 0.001$, $p < 0.001$, and $p < 0.01$, respectively).

Conclusion

A. jesdianum suggests attenuating CTX-associated liver toxicity by dampening oxidative stress and inflammatory responses, thereby supporting its prospective role as a natural cytoprotective adjunct in chemotherapy regimens.

Keywords: *Allium jesdianum*, Liver, Pro-inflammatory cytokines, Antioxidant enzymes.

Introductions

The use of drugs and chemical compounds in biological and clinical research is invariably associated with side effects (1). Cyclophosphamide (CTX) is an alkylating agent that possesses both pharmacological and toxic properties, affecting various organs (2). A significant adverse outcome of CTX administration is liver injury. The precise mechanisms underlying this toxicity are not fully understood, but oxidative stress, inflammation, and apoptosis are considered key contributors to CTX-related liver dysfunction. A primary side effect of CTX is the generation of reactive oxygen species (ROS), resulting in a reduction in the efficiency of antioxidant defense systems and subsequent damage to lipids, proteins, and DNA. In the liver, which plays a central role in metabolic and detoxification pathways, this oxidative stress can lead to mitochondrial damage, inflammation, and impaired liver function (3, 4). The molecular pathways implicated in CTX-induced hepatic oxidative stress are complex and interconnected. Elevated ROS levels and disturbances in antioxidant defense systems, such as glutathione pools and enzymatic scavengers, can promote lipid

peroxidation, depletion, or modification of antioxidant proteins, and DNA damage. These events activate multiple signaling cascades that mediate cellular responses to oxidative stress. Key pathways include the nuclear factor erythroid 2-related factor 2 (Nrf2) - antioxidant response element (ARE) axis, mitogen-activated protein kinase (MAPK) pathways, and cascades regulating apoptosis and inflammation. The interplay of these processes ultimately influences the extent of hepatic injury, modulating both the progression and potential resolution of liver damage (3, 5).

Allium jesdianum is widely recognized in traditional medicine and is a rich natural source of phenolic and antioxidant compounds, such as flavonoids and organosulfur compounds. Previous phytochemical studies have confirmed its strong free radical scavenging activity *in vitro*. Furthermore, biomedical research on *A. jesdianum* and related *Allium species* has demonstrated significant hepatoprotective effects in various models of liver injury. Key documented results include a marked reduction in lipid peroxidation levels, a significant increase in the activity of crucial antioxidant enzymes, and the suppression of pro-inflammatory cytokines (6, 7). For instance, in a model of acetaminophen-induced hepatotoxicity, a species from the same genus exhibited protection by restoring glutathione levels and mitigating histopathological damage. These established antioxidant and anti-inflammatory properties provide a strong pharmacological rationale for investigating *A. jesdianum* against CTX-induced liver injury, which is driven by similar pathways (6, 7).

In our previous study, *A. jesdianum* exhibited notable hepatoprotective effects against CTX-induced liver injury. Pretreatment with an oral *A. jesdianum* extract at 200 mg/kg daily for 14 days mitigated the liver damage induced by intraperitoneal (IP) administration of CTX at 20 mg/kg during the last five days. This was evidenced by the attenuation of CTX-induced elevations in liver enzymes and bilirubin, indicating a protective effect on the liver. Histopathological analysis supported these findings, revealing improved liver structure and reduced inflammation (8). However, determining the precise protective effects of *A. jesdianum against* CTX-induced liver injury requires more detailed analysis of molecular mechanisms. This study examines, for the first time, the molecular and biochemical mechanisms of CTX-induced hepatic oxidative stress and assesses the protective role of *A. jesdianum* using an integrated profile of oxidative stress markers including, thiobarbituric acid reactive substances (TBARS), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), alongside inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α). These elements provide new mechanistic insights and extend beyond our prior work.

Methods and materials

Plant Collection and Extract Preparation

A. jesdianum was collected in the spring of 2021 from the Bakhtiari Mountains and assigned the code (A-0138) by a specialist at Jundishapur University in Ahvaz. A hundred grams of dried whole plant powder were extracted with 300 mL of an 80:20 ethanol–water solvent using a maceration method. The resulting extract was concentrated with a rotary evaporator, freeze-dried, and then placed in a vacuum oven at 40°C for five days, after which it was stored at 4°C until needed (13).

Standardization of the extract

Total phenolic compounds were measured using the Folin–Ciocalteu spectrophotometric assay with gallic acid as the standard, and total flavonoid content was assessed via a colorimetric assay with quercetin as the standard (8).

Animals

NMRI mice (6–8 weeks old) were sourced from Tarbiat Modares University's Faculty of Medical Sciences. Baseline body weights ranged ~28–32 g. Mice were housed in polystyrene cages (5 per cage) and acclimated for one week in a controlled environment (20–22°C; 35% RH; 12 h light/dark) with ad libitum food and water. Tarbiat Modares University Animal Ethics Committee (ethical number IR.MODARES.AEC.1401.017) approved all animal procedures.

Treatment Protocols

Mice were randomly assigned to four groups (n = 5 per group):

Group 1: *A. jesdianum* group: Mice received oral administration of A. jesdianum extract at 200 mg/kg daily for 14 consecutive days.

Group 2: *A. jesdianum* + CTX group: Mice

were administered 200 mg/kg *A. jesdianum* extract orally for 14 days, with intraperitoneal (IP) injection of CTX at 20 mg/kg during the last 5 days.

Group 3: CTX group (positive control): Mice received an IP injection of CTX at 20 mg/kg for 5 consecutive days.

Group 4: Negative control group: Mice were administered oral normal saline daily for 14 days.

We selected the dosages and treatment durations based on previously reported studies to ensure consistency and reliability of the experimental outcomes. Those prior investigations demonstrated that the chosen doses were non-toxic when administered in isolation and exhibited protective effects across multiple organs, thereby supporting the rationale for applying these parameters in the CTX model to evaluate the hepatoprotective efficacy of *A. jesdianum* (8, 9).

Tissue Collection

On day 14, two hours after the final dose, the animals were sacrificed by spinal cord transection. This time point was chosen to ensure sufficient time for the final doses of both the extract and CTX to exert their full biological effects and to capture the ensuing acute biochemical responses.

The liver was carefully dissected, rinsed with ice-cold isotonic saline to remove blood, and then prepared for assessment of inflammatory cytokine parameters, lipid peroxidation, and antioxidant enzyme activity.

Malondialdehyde level

Malondialdehyde (MDA) level, as a marker of lipid peroxidation, was determined using the thiobarbituric acid (TBA) assay kit (Nalondi™ Lipid Peroxidation (MDA) Assay Kit, Navand Salamat, Iran) per the manufacturer's instructions (10).

Antioxidant enzyme activities

Liver antioxidant enzyme activities, such as SOD (U/ml or mg protein), CAT (nmol/min/mL), and GSH-Px (nmol/min/mL), were assessed using commercial assay kits (Nasdox™–Superoxide Dismutase Assay Kit, Navand Salamat, Iran; Nactaz™-Catalase Enzyme Activity assay kit (0-75), Navand Salamat, Iran; Glutathione Peroxidase Assay Kit (0-100), Navand Salamat, Iran, respectively) according to the manufacturers' protocols (11).

Inflammatory cytokine parameters

Liver inflammatory cytokines levels (pg/ml), including IL-6, IL-1β, and TNF-α, were measured using commercial ELISA kits according to the manufacturers' protocols (KPG-MIL6, Karmania Pars Gene, Iran; KPG-MIL1b, Karmania Pars Gene, Iran, and KPG-M, TNF-α, Karmania Pars Gene, Iran, respectively). Standard ranges of the kits were 0-200 pg/ml (12).

Statistical analyses

All data are expressed as mean ± standard deviation (SD). Before parametric analysis, the normality of the data distribution for each group was confirmed using the Shapiro-Wilk test. Upon confirmation of normality, the data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using Prism version 10.

Results

Liver lipid peroxidation

Figure 1 shows that the administration of CTX resulted in a significant rise in the levels of liver thiobarbituric acid reactive substances (TBARS) when compared to the negative control ($P < 0.001$). Conversely, pretreatment with *A. jesdianum* significantly reduced in TBARS levels within the treated group.

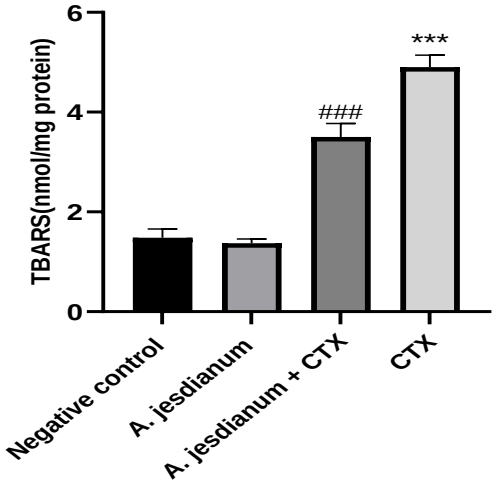

Figure 1. Effect of *A. jesdianum* on liver lipid peroxidation. Data are presented as mean ± SD (n = 5). Statistical analyses were performed using the Tukey-Kramer post-hoc test. *⁎⁎P < 0.001 vs. negative control (normal saline); ###P < 0.001 vs. CTX group. CTX: Cyclophosphamide; TBARS: Thiobarbituric acid reactive substances.

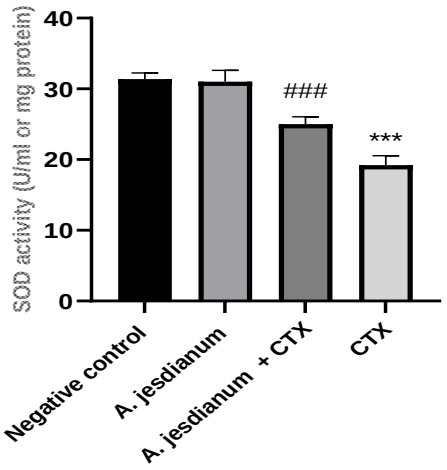

Figure 2. Effect of *A. jesdianum* on liver superoxide dismutase (SOD) activity. Data are presented as mean ± SD (n = 5). Statistical analyses were performed using the Tukey-Kramer post-hoc test. ***P < 0.001 vs. negative control (normal saline); ###P < 0.001 vs. CTX group. CTX: Cyclophosphamide; SOD: Superoxide dismutase.

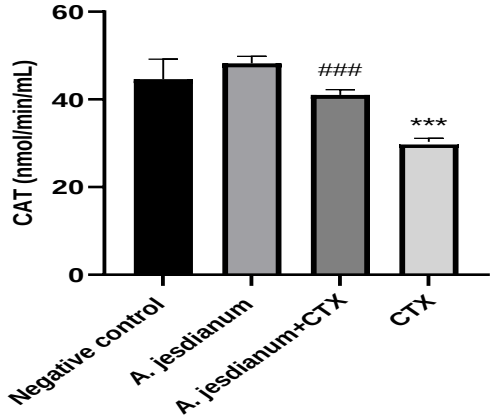

Figure 3. Effect of *A. jesdianum* on liver catalase (CAT) activity. Data are presented as mean ± SD (n = 5). Statistical analyses were performed using the Tukey-Kramer post-hoc test. ***P < 0.001 vs. negative control (normal saline); ###P < 0.001 vs. CTX group. CAT: Catalase; CTX: Cyclophosphamide.

Antioxidant enzymes assessments

SOD activity

Figure 2 illustrates that the activity levels of SOD were significantly lower in the CTX group compared to the negative control group in liver tissue ($p < 0.001$). The administration of *A. jesdianum* extract led to a significant increase in SOD activity in this tissue ($p < 0.001$).

CAT activity

CAT activity was found to be significantly reduced in the CTX group relative to the negative control ($p < 0.001$), while treatment with *A. jesdianum* statistically significantly enhanced CAT activity ($p < 0.001$) (Figure 3).

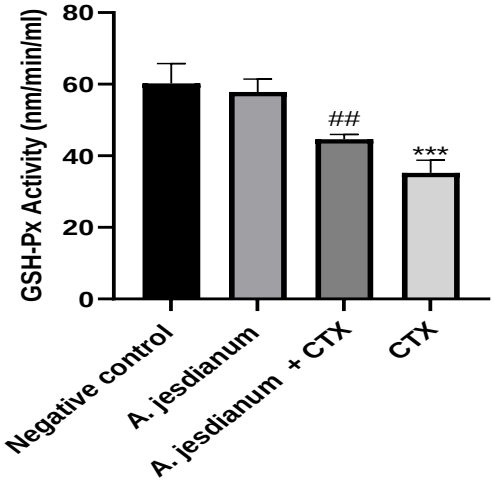

Figure 4. Effect of *A. jesdianum* on liver glutathione peroxidase (GSH-Px) activity. Data are presented as mean ± SD (n = 5). Statistical analyses were performed using Tukey-Kramer post-hoc test. ***P < 0.001 vs. negative control (normal saline); ##P < 0.01 vs. CTX group. CTX: Cyclophosphamide; GSH-Px: Glutathione peroxidase.

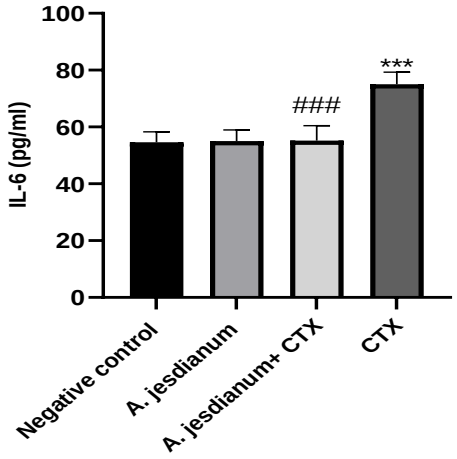

Figure 5. Effect of *A. jesdianum* on liver interleukin-6 (IL-6) levels. Data are presented as mean ± SD (n = 5). Statistical analyses were performed using the Tukey-Kramer post-hoc test. ***P < 0.001 vs. negative control (normal saline); ###P < 0.001 vs. CTX group. CTX: Cyclophosphamide; IL-6: Interleukin-6.

GSH-Px activity

As shown in Figure 4, the activity of GSH-Px was found to be significantly reduced in the CTX group compared to the negative control group ($p < 0.001$). However, treatment with *A. jesdianum* statistically significantly restored GSH-Px activity, resulting in a marked increase in enzyme level ($p < 0.01$).

Inflammatory cytokine parameters

IL-6 Level

As illustrated in Figure 5, administration of CTX resulted in a significant increase in IL-6

levels in liver tissue ($p < 0.001$). In contrast, pretreatment with *A. jesdianum* led to a notable reduction in IL-6 levels ($p < 0.001$), suggesting that *A. jesdianum* statistically significantly mitigates inflammation associated with CTX administration.

TNF-α Level

Figure 6 demonstrates that CTX administration significantly elevated TNF-α levels in liver tissue ($p < 0.001$); however, pretreatment with *A. jesdianum* statistically significantly decreased TNF-α levels decreased TNF-α level ($p < 0.001$).

IL-1β Level

The data presented in Figure 7 show that CTX administration significantly increased IL-1β level in liver tissue ($p < 0.001$). Pretreatment with *A. jesdianum* statistically significant reduced IL-1β levels ($p < 0.001$).

Discussion

This study significantly advances our understanding of the hepatoprotective properties of *A. jesdianum*, building on previous findings to elucidate the intricate biochemical and molecular mechanisms underlying its protection against CTX-induced hepatic injury. The administration of CTX resulted in marked elevation of liver enzymes and bilirubin levels, established biomarkers of hepatic damage, which are directly linked to the oxidative stress and inflammatory cascades triggered by this chemotherapeutic agent. Histopathological examinations provided further confirmation, revealing substantial architectural disorganization, necrotic foci, and pronounced inflammatory cell infiltration in the livers of CTX-treated animals (8). The pre-emptive introduction of *A. jesdianum* extract prior to CTX challenge demonstrated a notable and significant preservation of hepatic architecture and function, thereby affirming its potential as a valuable therapeutic agent.

The protective efficacy of *A. jesdianum* is profoundly rooted in its potent capacity to augment the endogenous antioxidant defense system, which is critically compromised by CTX. Our data reveal a significant suppression in the activities of pivotal antioxidant enzymes following CTX exposure (13). SOD, a first-line enzymatic defense that catalyzes the critical dismutation of superoxide radicals ($O_2^{\bullet -}$) into hydrogen peroxide and oxygen (14), was severely diminished, indicating a state of overwhelmed redox homeostasis (Figure 2) (15). Concurrently, CAT activity, which is indispensable for the detoxification of hydrogen peroxide (H_2O_2), a potentially harmful metabolic by-product, was also significantly impaired in the CTX group (Figure 3) (16). A parallel decline was observed in GSH-Px, a key enzyme in the reduction of lipid hydroperoxides and the protection of cellular membranes from oxidative degradation, as depicted in Figure 4 (17). The administration of *A. jesdianum* extract effectively counteracted these deficits, robustly restoring the activities of SOD, CAT, and GSH-Px. This collective restoration underscores the extract's powerful capability to mitigate oxidative injury by reinforcing the cellular machinery responsible for neutralizing reactive oxygen species and maintaining redox equilibrium (18, 19).

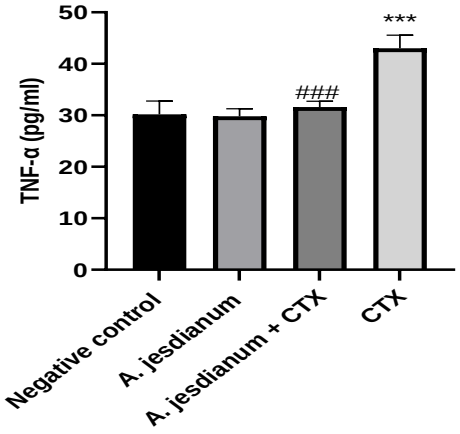

Figure 6. Effect of *A. jesdianum* on liver tumor necrosis factor-α (TNF-α) levels. Data are presented as mean ± SD (n = 5). Statistical analyses were performed using the Tukey-Kramer post-hoc test. ***P < 0.001 vs. negative control (normal saline); ###P < 0.001 vs. CTX group. CTX: Cyclophosphamide; TNF-α: Tumor necrosis factor-α.

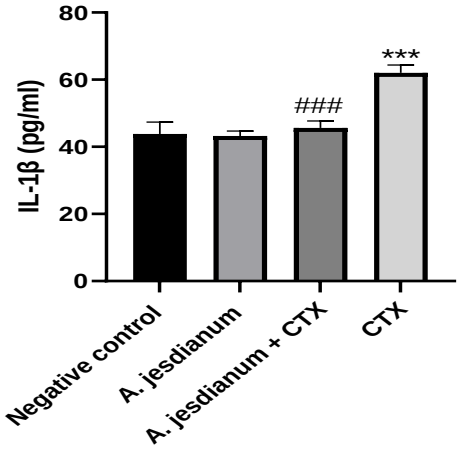

Figure 7. Effect of *A. jesdianum* on liver interleukin-1β (IL-1β) levels. Data are presented as mean ± SD (n = 5). Statistical analyses were performed using the Tukey-Kramer post-hoc test. ***P < 0.001 vs. negative control (normal saline); ###P < 0.001 vs. CTX group. CTX: Cyclophosphamide; IL-1β: Interleukin-1β.

Beyond its antioxidant prowess, *A. jesdianum* manifested profound anti-inflammatory effects, addressing another core pathway of CTX-induced hepatotoxicity. The CTX challenge provoked a robust pro-inflammatory response, characterized by a significant surge in the levels of key cytokines, including IL-6, TNF-α, and IL-1β. These cytokines are central mediators of the inflammatory cascade that amplifies tissue injury (20). The ability of *A. jesdianum* to significantly attenuate the levels of IL-6 (Figure 5), TNF-α (Figure 6), and IL-1β (Figure 7) strongly positions it as an effective anti-inflammatory agent. This attenuation not only signifies a direct reduction in inflammatory-driven liver damage but also suggests a potential modulation of upstream signaling pathways that govern the expression of these cytokines (21, 22).

The observed hepatoprotective, antioxidative, and anti-inflammatory properties of *A. jesdianum* resonate strongly with the well-documented pharmacological profile of the *Allium* genus. It is highly plausible that *A. jesdianum* contains a rich repertoire of bioactive constituents, such as organosulfur compounds, flavonoids (including potential quercetin derivatives), tannins, and saponins, which have been extensively reported in related species to mediate similar effects (23, 24). For instance, components isolated from onion (*Allium cepa*) have been shown to suppress cyclooxygenase (COX) and lipoxygenase (LOX) activities, thereby downregulating the synthesis of pro-inflammatory eicosanoids (25, 26). Similarly, *Allium flavum* extracts demonstrate inhibitory effects on COX-1 and 12-LOX (27), while other species like *Allium schoenoprasum* and *Allium hookeri* effectively attenuate nitro-oxidative stress and inhibit nuclear factor kappa B (NF-κB)–driven expression of inducible nitric oxide synthase (iNOS) and COX-2, consequently reducing the production of TNF-α and IL-6 (28, 29). Collectively, these reports suggest that the anti-inflammatory effects of *A. jesdianum* may involve both direct free-radical scavenging and the downregulation of canonical inflammatory signaling pathways, including NF-κB and MAPK. This dual mechanism would synergistically complement its demonstrated antioxidant activities (e.g., restoration of SOD, CAT, GSH-Px) to comprehensively counteract CTX-induced hepatic injury (23, 30, 31).

Limitations and Future Perspectives

While promising, this study has limitations that must be acknowledged. The use of a single, preventive dose, the lack of sex-based analysis despite known dimorphism in drug response, and the absence of long-term data constrain the immediate translational impact of our findings. A paramount question for clinical relevance is whether *A. jesdianum* interferes with CTX's anti-tumor efficacy (32). The same antioxidant and anti-inflammatory mechanisms that protect the liver could potentially shield cancer cells. Therefore, future research must prioritize:

Pharmacokinetic Interaction: Assessing the extract's influence on cytochrome P450 enzymes (e.g., CYP2B6, CYP3A4) critical for CTX activation and metabolism (33).

Tumor Efficacy: Directly testing the combination in tumor-bearing models to ensure the extract does not compromise CTX's chemotherapeutic potency.

Comprehensive Safety: Establishing the safety profile of *A. jesdianum* itself through chronic toxicity studies.

Addressing these challenges is essential to advance *A. jesdianum* as a viable adjunctive therapy, ensuring hepatoprotection without sacrificing oncological outcomes.

Conclusion

In conclusion, the findings of this study substantiate the protective effects of *A. jesdianum* against CTX-induced liver injury through a multifaceted approach involving the enhancement of antioxidant enzyme activity and the suppression of inflammatory cytokines. Nevertheless, a more comprehensive investigation into the specific molecular pathways involved, as well as the influence of dosing and timing of *A. jesdianum* treatment is warranted for a deeper understanding of its therapeutic potential. Future studies should aim to elucidate these mechanisms further, potentially paving the way for the development of *A. jesdianum* as a viable adjunct therapy in the management of chemotherapy-induced hepatic toxicity.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

References

1. Ingegneri M, Smeriglio E, Zebbiche Y, Cornara L, Visalli L, Smeriglio A, Trombetta D. The Dark Side of "Smart Drugs": Cognitive Enhancement vs. Clinical Concerns. Toxics. 2025;13(4):247.
2. Rajput SK, Singh S. Chapter 45 - The influence of alkylating agent on environment: Cyclophosphamide. In: Chawla M, Singh J, Kaushik RD, editors. Hazardous Chemicals. Academic Press; 2025. p. 629-43.
3. Sharata EE, Attya ME, Khalaf MM, Rofaeil RR, Hemeida RAM, Abo-Youssef AM. Unraveling chemotherapy-evoked hepatic dysfunction: a deep dive into cyclophosphamide-related liver injury. Naunyn Schmiedebergs Arch Pharmacol. 2025.
4. Cichoż-Lach H, Michalak A. Oxidative stress as a crucial factor in liver diseases. World J Gastroenterol. 2014;20(25):8082-91.
5. Allameh A, Niayesh-Mehr R, Aliarab A, Sebastiani G, Pantopoulos K. Oxidative Stress in Liver Pathophysiology and Disease. Antioxidants (Basel). 2023;12(9).
6. Sohrabinezhad Z, Dastan D, Asl SS, Nili-Ahmadabadi A. Allium Jesdianum Extract Improve Acetaminophen-Induced Hepatic Failure through Inhibition of Oxidative/Nitrosative Stress. J Pharmacopuncture. 2019;22(4):239-47.
7. Shamsipour Nehzomi Z, Shirani K. A comprehensive review of the pharmacological properties and medicinal uses of Allium jesdianum Boiss. & Buhse. J Med Plants. 2024;23(90):1-16.
8. Rezaei A, Yousefsani BS, Omidi A, Shirani K. Exploring the immune-boosting and hepatoprotective potential of Allium jesdianum against cyclophosphamide-induced toxicity in mice: A promising approach for immunomodulation. Avicenna J Phytomed. 2025;15(4):1366-78.
9. Keshavarzipoor K, Soodi M, Shirani K. Investigating the effects of hydroalcoholic extract of the Allium jesdianum on humoral and cellular indicators of the immune system in a mouse model stimulated with sheep erythrocyte Immunogen compared to Levamisole. Res Med. 2024;47(4):9-21.
10. Aguilar Diaz De Leon J, Borges CR. Evaluation of Oxidative Stress in Biological Samples Using the Thiobarbituric Acid Reactive Substances Assay. J Vis Exp. 2020(159).
11. Ismail NA, Okasha SH, Dhawan A, Abdel-Rahman AO, Shaker OG, Sadik NA. Antioxidant enzyme activities in hepatic tissue from children with chronic cholestatic liver disease. Saudi J Gastroenterol. 2010;16(2):90-4.
12. Hatipoglu D, Keskin E. The effect of curcumin on some cytokines, antioxidants and liver function tests in rats induced by Aflatoxin B1. Heliyon. 2022;8(7):e09890.
13. Bouyahya A, El Menyiy N, Oumeslakht L, El Allam A, Balahbib A, Rauf A, et al. Preclinical and Clinical Antioxidant Effects of Natural Compounds against Oxidative Stress-Induced Epigenetic Instability in Tumor Cells. Antioxidants (Basel). 2021;10(10).
14. Zheng M, Liu Y, Zhang G, Yang Z, Xu W, Chen Q. The Applications and Mechanisms of Superoxide Dismutase in Medicine, Food, and Cosmetics. Antioxidants (Basel). 2023;12(9).
15. Ibrahim KM, Darwish SF, Mantawy EM, El-Demerdash E. Molecular mechanisms underlying cyclophosphamide-induced cognitive impairment and strategies for neuroprotection in preclinical models. Mol Cell Biochem. 2024;479(8):1873-93.
16. Rasheed Z. Therapeutic potentials of catalase: Mechanisms, applications, and future perspectives. Int J Health Sci (Qassim). 2024;18(2):1-6.
17. Anwar S, Alrumaihi F, Sarwar T, Babiker AY, Khan AA, Prabhu SV, Rahmani AH. Exploring Therapeutic Potential of Catalase: Strategies in Disease Prevention and Management. Biomolecules. 2024;14(6):697.
18. Dai X, Huang Z, Lyu R. Free Radicals in Health and Disease. MedComm (2020). 2025;6(10):e70396.
19. Razavi-Azarkhiavi K, Jafarian AH, Abnous K, Razavi BM, Shirani K, Zeinali M, et al. The Comparison of Biodistribution, Efficacy and Toxicity of Two PEGylated Liposomal Doxorubicin Formulations in Mice Bearing C-26 Colon Carcinoma: a Preclinical Study. Drug Res (Stuttg). 2016;66(06):330-6.
20. Bhol NK, Bhanjadeo MM, Singh AK, Dash UC, Ojha RR, Majhi S, et al. The interplay between cytokines, inflammation, and antioxidants: mechanistic insights and therapeutic potentials of various antioxidants and anti-cytokine compounds. Biomed Pharmacother. 2024;178:117177.
21. Kandilarov I, Gardjeva P, Georgieva-Kotetarova M, Zlatanova H, Vilmosh N, Kostadinova I, et al. Effect of Plant Extracts Combinations on TNF-α, IL-6 and IL-10 Levels in Serum of Rats Exposed to Acute and Chronic Stress. Plants. 2023;12(17):3049.
22. Nikkhah E, Shirani K, Rezaee R, Karimi G. Protective effects of taurine against hepatotoxicity induced by pharmaceuticals and environmental chemicals. Toxicol Environ Chem. 2021;103(1):56-84.
23. Singh N, Gusain A, Nigam M, Mishra AP. The pharmacological and therapeutic versatility of Allium species: a comprehensive exploration of bioactive constituents and biological activities. Discov Appl Sci. 2025;7(4):349.
24. Petropoulos SA, Di Gioia F, Polyzos N, Tzortzakis N. Natural antioxidants, health effects and bioactive

properties of wild Allium species. Curr Pharm Des. 2020;26(16):1816-37.

25. Marefati N, Ghorani V, Shakeri F, Boskabady M, Kianian F, Rezaee R, Boskabady MH. A review of anti-inflammatory, antioxidant, and immunomodulatory effects of Allium cepa and its main constituents. Pharm Biol. 2021;59(1):285-300.
26. Elattar MM, Hammoda HM, Ghareeb DA, Abdulmalek SA, Abdelrahim FA, Seif IA, et al. Insights into bioactive constituents of onion (Allium cepa L.) waste: a comparative metabolomics study enhanced by chemometric tools. BMC Complement Med Ther. 2024;24(1):271.
27. Simin N, Orcic D, Cetojevic-Simin D, Mimica-Dukic N, Anackov G, Beara I, et al. Phenolic profile, antioxidant, anti-inflammatory and cytotoxic activities of small yellow onion (Allium flavum L. subsp. flavum, Alliaceae). LWT-Food Sci Technol. 2013;54(1):139-46.
28. Parvu AE, Parvu M, Vlase L, Miclea P, Mot AC, Silaghi-Dumitrescu R. Anti-inflammatory effects of Allium schoenoprasum L. leaves. J Physiol Pharmacol. 2014;65(2):309-15.
29. Kim C-H, Lee M-A, Kim TW, Jang J, Kim H. Anti-inflammatory Effect of Allium hookeri Root Methanol Extract in LPS-induced RAW264.7 Cells. J Korean Soc Food Sci Nutr. 2012;41.
30. Jang JY, Lee MJ, You BR, Jin JS, Lee SH, Yun YR, Kim HJ. Allium hookeri root extract exerts anti-inflammatory effects by nuclear factor-κB down-regulation in lipopolysaccharide-induced RAW264.7 cells. BMC Complement Altern Med. 2017;17(1):126.
31. Kamranfar F, Jaktaji RP, Shirani K, Jamshidi A, Samiei F, Arjmand A, et al. Protective effect of a standardized Allium jesdianum extract in an Alzheimer's disease induced rat model. Neurosci Lett. 2023;815:137491.
32. Soldin OP, Mattison DR. Sex Differences in Pharmacokinetics and Pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143-57.
33. Xie HJ, Yasar U, Lundgren S, Griskevicius L, Terelius Y, Hassan M, Rane A. Role of polymorphic human CYP2B6 in cyclophosphamide bioactivation. Pharmacogenomics J. 2003;3(1):53-61.