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Evaluation of the Effects of Peiminine on Disease Activity Indices and Inflammatory Markers in an Experimental Model of Autoimmune Hepatitis

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ABSTRACT

Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease that can progress to cirrhosis and liver failure if untreated. Current therapies, mainly corticosteroids, are effective but limited by adverse effects and incomplete responses, prompting the search for safer alternatives. Peiminine, an alkaloid derived from Fritillaria species, has demonstrated anti-inflammatory and antioxidant properties in several disease models. This study evaluated its efficacy in a concanavalin A (ConA)–induced mouse model of AIH.

Male C57BL/6 mice were divided into six groups, including ConA-injured animals, and treatment groups receiving peiminine (3 mg/kg, i.p.), prednisolone (10 mg/kg, i.p.), or their combination.

ConA injection caused sharp increases in ALT (↑ 5.4-fold), AST (↑ 4.8-fold), and ALP (↑ 3.9-fold), alongside marked elevations in MPO activity, nitric oxide, and pro-inflammatory cytokines (TNF-α, IL-6, IFN-γ). Peiminine significantly reversed these alterations-reducing ALT, AST, and ALP by 65% to 75% and restoring IL-4, TGF-β, and SOD activity toward normal values. Pre-treatment provided stronger protection than post-treatment, and outcomes were comparable to those of prednisolone, with combination therapy yielding the greatest improvement across all indices.

These findings indicate that peiminine mitigates immune-mediated hepatic injury by modulating cytokines, reducing oxidative stress, and maintaining liver integrity. Peiminine may represent a promising preventive or adjunct therapy for AIH, warranting further mechanistic and long-term investigations.

Keywords: Autoimmune hepatitis; Combination therapy; Immunomodulation; Oxidative stress; Peiminine

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiology, characterized by circulating autoantibodies, hypergammaglobulinemia, and progressive hepatic inflammation. The disease is believed to result from a complex interplay between genetic predisposition and environmental triggers, leading to aberrant activation of the immune system and sustained hepatocellular injury.[1] Epidemiological studies report a global prevalence of

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approximately 10–25 cases per 100 000 individuals, with an annual incidence of 1–2 new cases per 100 000.[2] Notable geographical variations have been observed, with higher prevalence rates-up to 30 cases per 100 000in Northern Europe and North America compared to most Asian regions.[3]

If left untreated, AIH often progresses to cirrhosis, liver failure, and death within 5 years. In contrast, appropriately treated patients typically achieve long-term survival with preserved quality of life.[4] Current standard therapy, based on corticosteroids with or without azathioprine, is effective in many patients; however, drug resistance, adverse effects, and incomplete responses remain significant clinical challenges.[5] This has prompted growing interest in alternative or adjunctive therapeutic strategies that can modulate immune responses and limit hepatic injury with improved safety profiles.

Peiminine is an alkaloid compound derived primarily from the bulbs of *Fritillaria* species, widely used in traditional Chinese medicine. Over the past decade, peiminine has gained considerable attention due to its broad spectrum of pharmacological activities, particularly its anti-inflammatory, anticancer, and immunomodulatory properties.

Mechanistic studies have revealed that peiminine exerts anti-inflammatory effects by inhibiting key signaling cascades such as AKT/NF-κB (protein kinase B/nuclear factor κB), ERK1/2 (extracellular signal-regulated protein kinases 1 and 2), and p38 MAPK (mitogen-activated protein kinase), leading to decreased production of proinflammatory cytokines, including IL-1β, TNF-α, and IL-6.[6] Beyond its anti-inflammatory role, peiminine has demonstrated pro-apoptotic and autophagy-inducing activities in several cancer cell models. For instance, it induces apoptosis in hepatocellular carcinoma (HepG2) cells by activating caspase signaling[7] and suppresses colorectal cancer progression by regulating apoptosis, autophagy, and metabolic pathways.[8] Furthermore, peiminine exhibits protective effects in inflammatory and degenerative diseases. In mouse articular chondrocytes, it was shown to inhibit IL-1β–induced inflammatory responses and significantly ameliorate osteoarthritis in vivo.[9] These findings suggest that peiminine regulates inflammation through multiple signaling networks while also modulating cellular survival and death pathways.

Given the central role of aberrant immune activation and inflammatory cytokine release in the pathogenesis of AIH, peiminine emerges as a promising candidate for therapeutic evaluation. However, its potential hepatoprotective and immunomodulatory effects in the context of AIH remain largely unexplored. Therefore, this study aims to investigate the effects of peiminine on disease activity indices and inflammatory markers in an experimental model of AIH, with a focus on its ability to modulate immune-inflammatory pathways. Taken together, we hypothesized that peiminine would mitigate autoimmune-mediated hepatic injury by attenuating proinflammatory cytokine release, enhancing antioxidant defenses, and restoring immune balance. Furthermore, we anticipated that peiminine, either alone or in combination with prednisolone, would reduce disease activity indices in a ConA-induced model of AIH.

MATERIALS AND METHODS

Animals

Male C57BL/6 mice (6–8 weeks old) were purchased from the Pasteur Institute of Iran. Animals were housed in the Laboratory Animal Facility of Baqiyatallah University of Medical Sciences for 1 week prior to experimentation to allow for acclimatization. Mice had ad libitum access to standard chow and water under controlled environmental conditions (22 ± 2°C, 12-hour light/dark cycle, 55% ± 5% humidity). All experimental procedures were conducted in accordance with institutional ethical guidelines for animal care and use.

Induction of AIH Model

An acute AIH model was established using ConA. Briefly, mice received a single intravenous injection of ConA (20 mg/kg; Sigma-Aldrich) via the lateral tail vein. Prior to injection, mice were warmed under an infrared lamp, and tails were immersed in warm water (35–37°C) to dilate tail veins. Injections were performed using insulin syringes to ensure accuracy and minimal tissue injury. Following ConA administration, animals were monitored closely for signs of distress and then randomly assigned to the designated experimental groups.

Experimental Groups

A total of 6 groups were included in the study:

1. Control group: Received phosphate-buffered saline (PBS; 100 μL, intraperitoneal [i.p.]) daily until the

end of the study with ConA injection.

2. Peiminine pretreatment group: Received peiminine (3 mg/kg, i.p.) daily for 10 consecutive days prior to ConA injection and continued daily administration until the end of the study.

3. Peiminine post-treatment group: Received peiminine (3 mg/kg, i.p.) starting 4 hours after ConA injection and continued daily until the end of the study.

4. Prednisolone treatment group: Received prednisolone (10 mg/kg, i.p.) starting 4 hours after ConA injection and continued daily until the end of the study.

5. Combination treatment group with prednisolone and pretreatment with peiminine: Received peiminine (3 mg/kg, i.p.) daily for 10 consecutive days prior to ConA injection and continued daily administration until the end of the study; received prednisolone (10 mg/kg, i.p.) starting 4 hours after ConA injection and continued daily until the end of the study.

6. Combination treatment group with prednisolone and peiminine treatment: Received peiminine (3 mg/kg, i.p.) and prednisolone (10 mg/kg, i.p.) starting 4 hours after ConA injection and continued daily until the end of the study.

The peiminine dose (3 mg/kg) was selected based on previous in vivo studies reporting effective anti-inflammatory and antioxidant responses without signs of toxicity in mice.[6,9] This dose has been shown to significantly suppress NF-κB and MAPK activation while maintaining normal hepatic enzyme levels, supporting its suitability for evaluating hepatoprotective effects in the present model.

Sample Collection

After completing the grouping conditions, mice were euthanized with an intraperitoneal injection of ketamine/xylazine. Blood samples were collected via cardiac puncture, and sera were separated for biochemical and cytokine assays.

Biochemical and Inflammatory Marker Assays

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) activities were measured using commercial diagnostic kits (Mybiosource, Canada). Myeloperoxidase (MPO) activity, nitric oxide (NO) levels, and serum concentrations of IL-4, TNF-α, IL-6, IFN-γ, and TGF-β were quantified using commercially available enzyme-linked immunosorbent (ELISA) kits (Mybiosource, Canada and Elabscience, USA) according to the manufacturer's instructions.

Statistical Analysis

All data are expressed as mean ± standard deviation (SD). Statistical analyses were performed using SPSS software, version 26 (IBM, USA). Group comparisons were conducted using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. Each experimental group contained $n = 8$ mice, unless otherwise specified. A $p<0.05$ was considered statistically significant.

RESULTS

Serum Liver Enzyme Activities

To evaluate hepatocellular damage and cholestatic dysfunction, serum activities of ALT, AST, and ALP were assessed across all 6 groups (Figure 1). ConA administration caused a dramatic rise in all three enzymes ($p<0.05$). ALT showed the most pronounced elevation, consistent with its high specificity as a biomarker of hepatocyte necrosis. AST and ALP were also markedly elevated, reflecting mitochondrial injury and cholestatic stress, respectively. These findings confirmed the successful establishment of acute immune-mediated liver injury.

Peiminine pretreatment markedly reduced ALT, AST, and ALP activities compared to the ConA group ($p<0.05$). This suggests that pretreatment provided strong protection against hepatocyte membrane disruption and bile duct injury. Peiminine posttreatment also significantly decreased enzyme activities, though reductions were moderately less pronounced than pretreatment, suggesting a stronger prophylactic than therapeutic effect.

Interestingly, prednisolone treatment restored ALT, AST, and ALP levels to values nearly identical to those observed with peiminine pretreatment. This indicates that peiminine hepatoprotective potential is comparable to that of a standard corticosteroid therapy in this model.

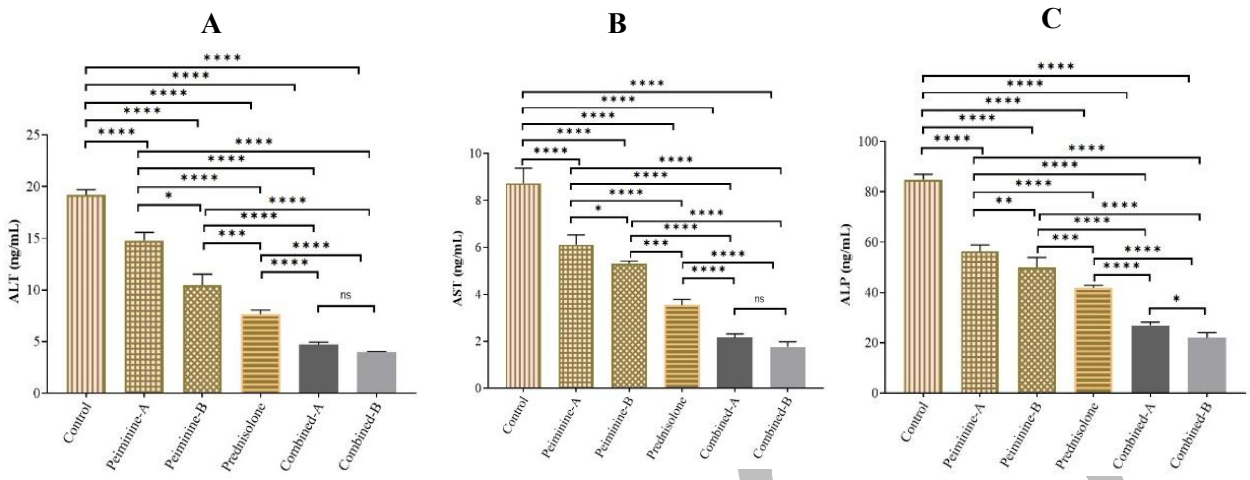

Figure 1. Effects of peiminine and prednisolone on serum liver enzyme activities in ConA-induced autoimmune hepatitis. A. ALT, B. AST, and C. ALP levels measured 12 hours after ConA injection. ConA caused sharp increases in all three enzymes. Peiminine (pre- > post-treatment) and prednisolone significantly reduced these elevations, while combination therapy produced the greatest normalization. Data are mean±SD (n=8 mice per group); p<0.05 vs ConA; † *p*<0.05 vs peiminine-post. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ConA: concanavalin A.

Myeloperoxidase Activity and Nitric Oxide Levels

To further probe inflammatory infiltration and nitrosative stress, MPO activity and NO levels were measured (Figure 2).

ConA administration resulted in a profound increase in both MPO and NO ($p<0.05$), indicative of excessive neutrophil accumulation and inducible nitric oxide synthase (iNOS) activation during hepatic inflammation.

Both peiminine regimens attenuated these increases. Pretreatment with peiminine significantly reduced MPO and NO, restoring them closer to baseline values, whereas posttreatment also reduced both markers but to a lesser extent. Prednisolone treatment closely mirrored peiminine pretreatment, demonstrating its expected potent anti-inflammatory and anti-nitrosative effects.

Notably, the relative reduction in MPO was greater than that in NO across all treatments, suggesting that peiminine and prednisolone may be more effective at limiting neutrophil infiltration than suppressing NO generation directly.

Proinflammatory Cytokines

To assess systemic inflammatory responses, levels of TNF-α, IL-6, and IFN-γ were measured (Figure 2).

ConA challenge resulted in robust increases in TNF-α, IL-6, and IFN-γ ($p<0.05$), confirming the induction of a strong T_H1-type immune response. TNF-α, a central mediator of hepatocyte apoptosis, showed the steepest increase, while IL-6 and IFN-γ also rose sharply, reflecting both innate and adaptive immune activation.

Both peiminine interventions significantly reduced cytokine levels compared with ConA ($p<0.05$). Pretreatment with peiminine produced the most pronounced reductions, with TNF-α, IL-6, and IFN-γ nearing baseline values. Posttreatment also attenuated cytokine surges but to a lesser extent, again highlighting stronger preventive than therapeutic efficacy. Prednisolone administration achieved reductions comparable to peiminine pretreatment, validating its reference role.

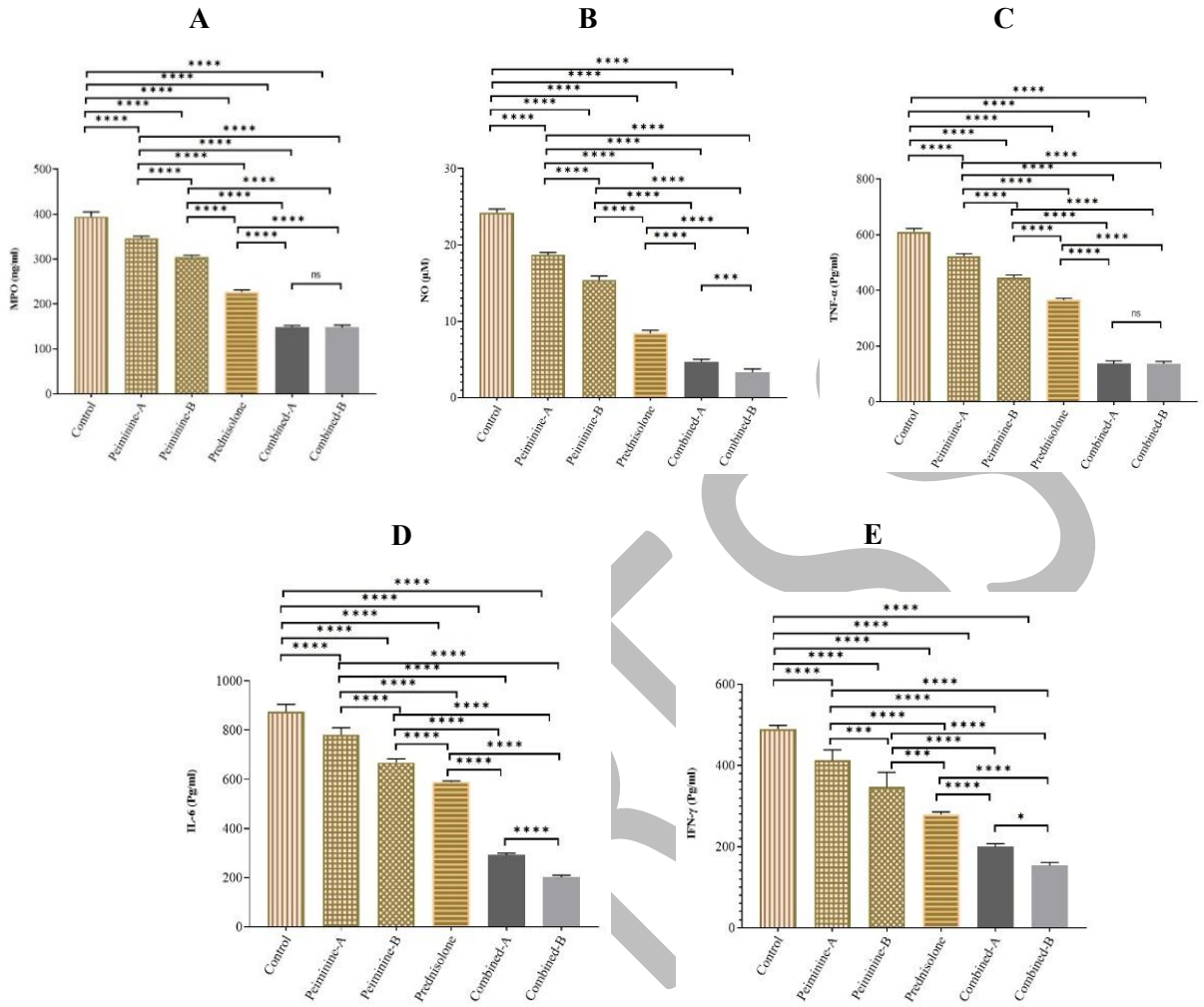

Figure 2. Peiminine and prednisolone attenuate inflammatory and nitrosative stress markers. A. MPO activity, B. NO concentration, C. TNF-α, D. IL-6, and E. IFN-γ levels. ConA markedly elevated all markers; peiminine and prednisolone each reduced inflammation and nitrosative stress, with the combination regimen showing the most pronounced suppression. Data are mean±SD (n=8); $p<0.05$ vs ConA. ConA: concanavalin A; IFN-γ: interferon γ; IL-6: interleukin 6; MPO: myeloperoxidase; NO: nitric oxide; TNF-α: tumor necrosis factor α.

This consistent pattern across cytokines underscores peiminine's capacity to blunt multiple arms of the inflammatory cascade, thereby limiting immune-mediated liver injury.

Anti-inflammatory Cytokines

IL-4, a representative T_H2 cytokine, was measured to evaluate counter-regulatory anti-inflammatory signaling (Figure 3).

ConA administration caused a significant reduction in IL-4 compared with controls ($p<0.05$), confirming suppression of anti-inflammatory signaling in favor of a T_H1-dominant response.

Both peiminine regimens significantly reversed IL-4 suppression compared with ConA. Pre-treatment elevated IL-4 to levels approaching those of the healthy and vehicle controls, while posttreatment produced a moderate but significant improvement. Prednisolone also increased IL-4, reaching values nearly equal to peiminine pretreatment.

These findings suggest that peiminine not only inhibits proinflammatory cytokines but also promotes anti-inflammatory mediators, thereby restoring immunological balance.

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TGF-β Levels

TGF-β, another immunomodulatory cytokine involved in regulatory T cell activity and tissue repair, was evaluated (Figure 3).

Treatment with peiminine significantly increased TGF-β compared to ConA. Pretreatment showed a greater restorative effect than post-treatment, though neither returned levels fully to control values. Prednisolone treatment also enhanced TGF-β to a comparable degree with peiminine pretreatment.

The partial restoration of TGF-β suggests that peiminine aids in re-establishing immune tolerance and repair mechanisms, although full normalization may require longer exposure or higher doses.

Oxidative Stress Marker (MDA Content)

Malondialdehyde (MDA), a marker of lipid peroxidation and oxidative stress, was markedly elevated in the ConA group (p<0.05; Figure 4).

Both peiminine pre- and post-treatment significantly reduced MDA compared with ConA (p<0.05). Pre-treatment yielded greater protection, reducing MDA almost to control values, whereas post-treatment achieved partial improvement. Prednisolone treatment showed reductions comparable to peiminine pretreatment, further supporting peiminine's strong antioxidant capacity.

Antioxidant Enzyme Activities

Finally, antioxidant defense was evaluated by measuring superoxide dismutase (SOD) activities (Figure 4). ConA treatment significantly depressed both enzymes compared with controls (p<0.05), indicating profound oxidative imbalance.

All therapeutic interventions enhanced antioxidant enzyme activities compared with ConA (p<0.05). Peiminine pretreatment produced the greatest recovery, with SOD activities approaching healthy control values. Posttreatment also improved enzyme activities significantly, though the extent of restoration was less than pretreatment. Prednisolone enhanced SOD to levels nearly equivalent to peiminine pretreatment, validating the robustness of peiminine's antioxidant defense.

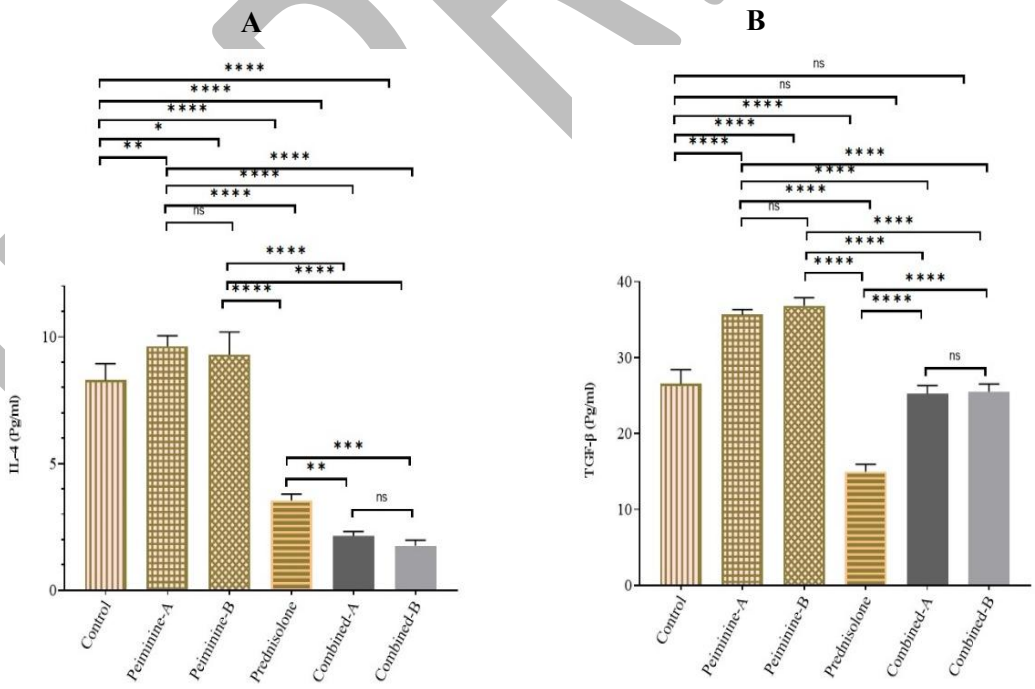

Figure 3. Restoration of anti-inflammatory cytokines by peiminine and prednisolone. A. IL-4 and B. TGF-β levels. Both cytokines were significantly reduced after ConA challenge but restored by peiminine and prednisolone. Combination therapy produced near-normal values, indicating recovery of anti-inflammatory balance. Data are mean±SD (n=8); p<0.05 vs ConA. ConA: concanavalin A; IL-4: interleukin 4; TGF-β: transforming growth factor β.

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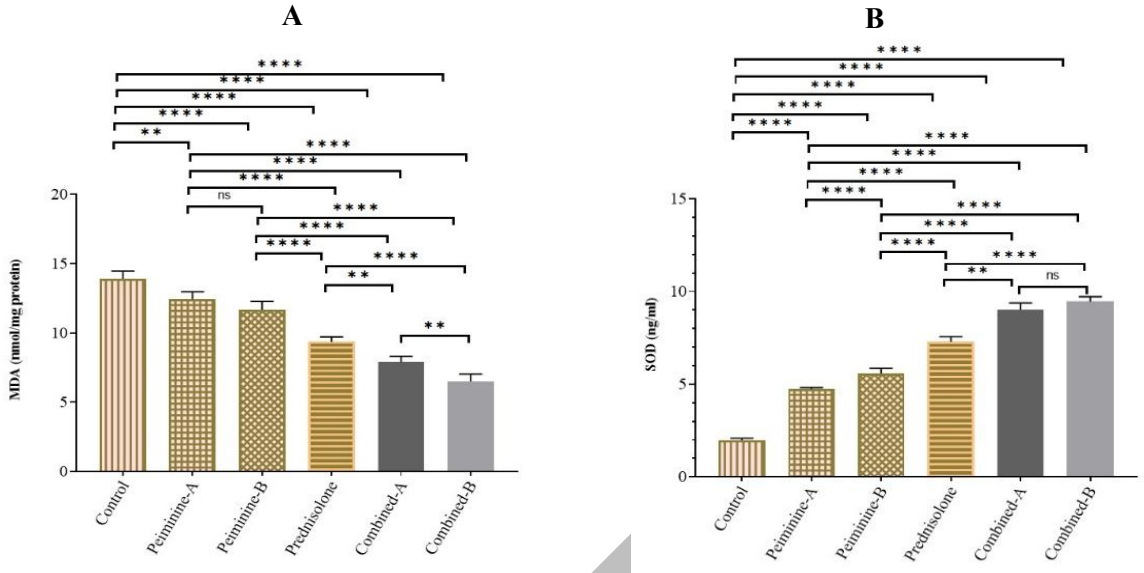

Figure 4. Peiminine and prednisolone reduce oxidative stress and preserve hepatic architecture. A. MDA content and B. SOD activity. ConA increased lipid peroxidation, reduced antioxidant capacity, and caused extensive necrosis and inflammation. Data are mean±SD (n=8); p<0.05 vs ConA. ConA: concanavalin A; MDA: malondialdehyde; SOD: superoxide dismutase.

Overall Disease Activity Indices

Taken together, the biochemical (ALT, AST, ALP), inflammatory (MPO, NO, TNF-α, IL-6, IFN-γ), anti-inflammatory (IL-4, TGF-β), and oxidative-stress (MDA, SOD) readouts constitute the study's disease activity indices. Relative to the ConA group, peiminine (pre->post-treatment), prednisolone, and especially their combination improved these indices across multiple domains (p<0.05 for each marker vs ConA).

DISCUSSION

In the present study, peiminine demonstrated strong hepatoprotective and immunomodulatory properties in a ConA-induced AIH model. Pretreatment with peiminine was more effective than posttreatment, as evidenced by greater reductions in serum ALT, AST, and ALP activities. This suggests that prophylactic administration can effectively prevent hepatocyte necrosis and cholestatic dysfunction, while therapeutic intervention after injury provides partial but significant benefits. Interestingly, the efficacy of peiminine was comparable to that of prednisolone, a standard corticosteroid treatment for immune-mediated liver injury.

The observed reductions in MPO activity and NO levels indicate that peiminine suppresses neutrophil infiltration and nitrosative stress. Neutrophil accumulation and iNOS-derived NO are critical contributors to ConA-induced hepatocellular damage, and inhibition of iNOS activity is known to protect against this pathology.[10] These findings are consistent with recent descriptions of cytokine dynamics in Concanavalin A–induced acute liver injury.[11] Our findings align with reports that peiminine inhibits NF-κB and MAPK signaling, thereby decreasing iNOS expression and inflammatory mediator release.[6,9, 12,13]

Cytokine analysis further supports the anti-inflammatory effects of peiminine. TNF-α, IL-6, and IFN-γ were markedly elevated in the ConA group, consistent with the established role of these mediators in AIH pathogenesis.[14-16] Peiminine significantly lowered their levels, particularly with pre-treatment, suggesting that it suppresses both innate and adaptive immune activation. Importantly, peiminine also restored IL-4 and TGF-β levels, which were reduced following ConA challenge. Restoration of TGF-β is particularly relevant, as regulatory cytokines are essential for maintaining immune tolerance and limiting immune-mediated liver injury.[14-16]

The antioxidant capacity of peiminine was also evident. Elevated MDA levels and reduced SOD and CAT activities in the ConA group reflected lipid peroxidation and oxidative imbalance, both hallmark features of immune-mediated hepatitis. Peiminine pre-

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treatment almost normalized these parameters, while post-treatment offered partial protection. These results are in line with other antioxidant interventions, such as resveratrol and α-lipoic acid, which reduce lipid peroxidation, restore antioxidant enzyme activity, and alleviate ConA-induced hepatic injury.[17,18]

Collectively, these results indicate that peiminine exerts multifaceted hepatoprotective effects in AIH. The mechanisms appear to involve inhibition of pro-inflammatory cytokine release through NF-κB and MAPK suppression,[6,9,12,13] reduction of nitrosative stress by downregulating iNOS,[10] restoration of anti-inflammatory mediators such as IL-4 and TGF-β,[14-16] enhancement of antioxidant defenses,[17,18] and preservation of hepatic tissue architecture.[7,8,15] The comparable efficacy to prednisolone[19,20] underscores its potential as a preventive or therapeutic agent. Future investigations should focus on the molecular targets of peiminine in hepatocytes and immune cells, as well as long-term studies in chronic AIH models.

This study has several limitations. First, only a single dose of peiminine (3 mg/kg) was tested, which restricts assessment of dose–response relationships and pharmacodynamic range. Second, the study used an acute ConA-induced model that may not fully reflect chronic AIH pathophysiology. Third, mechanistic pathways were inferred from cytokine and oxidative-stress markers rather than direct gene or protein analyses (e.g., Western blotting or qPCR). Future studies should include multiple dosing regimens, molecular confirmation of signaling changes, and long-term experiments in chronic AIH models to strengthen translational relevance.

In this study, peiminine demonstrated strong hepatoprotective, anti-inflammatory, and antioxidant effects in a ConA-induced model of AIH. Both pre- and post-treatment with peiminine attenuated liver enzyme elevations, reduced oxidative stress, and modulated cytokine profiles, thereby limiting immune-mediated hepatocellular injury. Prophylactic administration produced superior outcomes compared with therapeutic intervention.

Importantly, when combined with prednisolone, peiminine provided additive benefits, achieving more profound reductions in pro-inflammatory cytokines and enhanced restoration of anti-inflammatory mediators compared with either agent alone.

These findings suggest that peiminine may serve as a translational candidate for adjunctive therapy in AIH, with potential to enhance corticosteroid efficacy while lowering required steroid doses and minimizing long-term complications. Further preclinical and pharmacokinetic studies are warranted to define its mechanism, safety profile, and applicability to chronic and human AIH models.

STATEMENT OF ETHICS

All experimental procedures involving animals were conducted in accordance with the guidelines of the Research Ethics Committees of Laboratory Animals-Baqiyatallah University of Medical Sciences (Approval Code: IR.BMSU.AEC.1403.030). Efforts were made to minimize animal suffering and to use the minimum number of animals required for valid statistical analysis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

All datasets generated or analyzed during the current study are available from the corresponding author on reasonable request

AI ASSISTANCE DISCLOSURE

Not applicable.

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