ORIGINAL RESEARCH

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# Protective Effects of Amantadine on Secondary Liver Injury Following Traumatic Brain Injury in an Experimental Rat Model

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## Abstract

### Objective
Traumatic brain injury (TBI) is known to trigger systemic inflammatory responses, leading to damage in distant organs such as the liver. Amantadine (AMA), an NMDA receptor antagonist, exhibits both anti-inflammatory and neuroprotective properties. This study investigated the protective effects of AMA against liver injury secondary to TBI in a rat model.

### Material and Method
Forty male Wistar albino rats were randomly assigned to four groups: Control, Trauma (TRA), TRA+AMA-1, and TRA+AMA-7. TBI was induced by the Marmarou weight-drop method. AMA (45 mg/kg/day, intraperitoneal) was administered for 1 and 7 days post-TBI. Liver tissues were harvested and evaluated via histopathological scoring and immunohistochemical analysis for tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interferon beta (IFN-β).

### Results
TBI significantly elevated hepatic expression of pro-inflammatory cytokines (IFN-β, IL-6, TNF-α) and caused marked histological damage, including hyperemia, hemorrhage, inflammation, and necrosis. AMA treatment markedly reduced these cytokine expressions and ameliorated histopathological alterations. The TBI+AMA-7 group exhibited substantial recovery compared to the TBI group, indicating an association between amantadine treatment and reduced histopathological liver injury.

### Conclusion
The trauma group demonstrated significantly higher histopathological liver injury scores compared with the control group. AMA treatment was associated with reduced histopathological alterations and lower immunoreactivity of pro-inflammatory cytokines compared with the untreated trauma group.

**Keywords:** Amantadine; cytokines; histopathology; liver inflammation; traumatic brain injury.

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## Introduction

Traumatic brain injury (TBI) imposes a substantial worldwide health burden, contributing markedly to morbidity as well as mortality (1, 2). Beyond the immediate neurological damage, TBI provokes complex systemic cascades that frequently culminate in secondary injury of peripheral organs—most notably the liver (3, 4). The systemic inflammatory response following TBI involves the release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interferon beta (IFN-β), which can disrupt hepatic microcirculation and cellular homeostasis, resulting in hepatocellular damage and dysfunction (5). Preclinical studies have suggested that systemic inflammatory responses following TBI may contribute to secondary injury in peripheral organs, including the liver (18).

Amantadine (AMA), an adamantane derivative, is known for its multifaceted pharmacological properties, including dopaminergic agonism, NMDA receptor antagonism, and anti-inflammatory effects (7). While traditionally used in the treatment of Parkinson's disease and fatigue in neurological conditions, recent research has explored its potential neuroprotective and systemic benefits (8). In traumatic-brain-injury models, AMA has been reported to temper neuroinflammatory responses, foster cognitive recovery, and suppress the release of pro-inflammatory signaling molecules. (9). These pharmacological attributes imply that AMA might confer hepatoprotective effects in the setting of TBI-induced secondary injury (10).

The present study investigates whether AMA can mitigate traumatic-brain-injury–induced liver damage in an experimental rat model. Histopathological assessments, including evaluations of hyperemia, hemorrhage, inflammation, and necrosis, were conducted alongside immunohistochemical analyses of key inflammatory markers (IFN-β, IL-6, and TNF-α).

## Material and Method

### Animals and Experimental Groups

Ethical approval for the experiment was obtained from the Suleyman Demirel University Local Animal Experiments Ethics Committee (Ethic No: 15.05.2025/514-05). A total of 40 adult male Wistar Albino rats weighing between 300–350 grams were included. Animals were randomly allocated to the experimental groups. Rats were housed in standard polypropylene cages under controlled environmental conditions (temperature: 21–22 °C; humidity: 55%; light/dark cycle: 12/12 h) with free access to standard rat chow and water. Following a 7-day acclimatization period, the animals were randomly assigned to four experimental groups (n=10 each).

### Drugs and Chemicals

Amantadine hydrochloride was obtained from Sigma-Aldrich (St. Louis, MO, USA) and prepared freshly before administration. The drug was dissolved in sterile physiological saline and administered intraperitoneally at a dose of 45 mg/kg. The selected dose of amantadine (45 mg/kg) was based on previously reported experimental studies demonstrating anti-inflammatory and neuroprotective effects in rodent models without inducing toxicity (28).

• *Control (Cont):* Under anesthesia, animals received 1 mL intraperitoneal (i.p.) saline. After 24 hours, liver tissues were collected post-sacrifice.

• *TRA:* Diffuse brain trauma was produced with the Marmarou impact-acceleration paradigm (50 g weight released from 2 m), followed by 1 mL i.p. saline. Animals were sacrificed at 24 hours, and liver tissues were collected (11).

• *TRA + AMA-1:* TBI was induced, followed by administration of 45 mg/kg i.p. AMA. After 24 hours, animals were sacrificed and liver tissues collected.

• *TRA + AMA-7:* Following TBI induction, animals were treated with 45 mg/kg i.p. AMA once daily for 7 days. Liver tissue samples were collected on day 7 after sacrifice.

The 7-day time point was selected to evaluate subacute hepatic alterations and potential recovery processes following traumatic brain injury.

The experimental groups, treatment protocols, and sacrifice time points are schematically illustrated in a timeline diagram (Figure 1).

To model head trauma, we employed the impact-acceleration paradigm, releasing a 50 g weight from a height of 2 m onto the skull (11).

The Marmarou impact-acceleration model is one of the most widely used and validated experimental models for diffuse traumatic brain injury in rodents. This model produces rapid acceleration–deceleration forces that mimic diffuse brain injury and trigger systemic inflammatory responses. Previous studies have demonstrated that traumatic brain injury can induce systemic cytokine release leading to secondary damage in peripheral organs, including the liver. There-

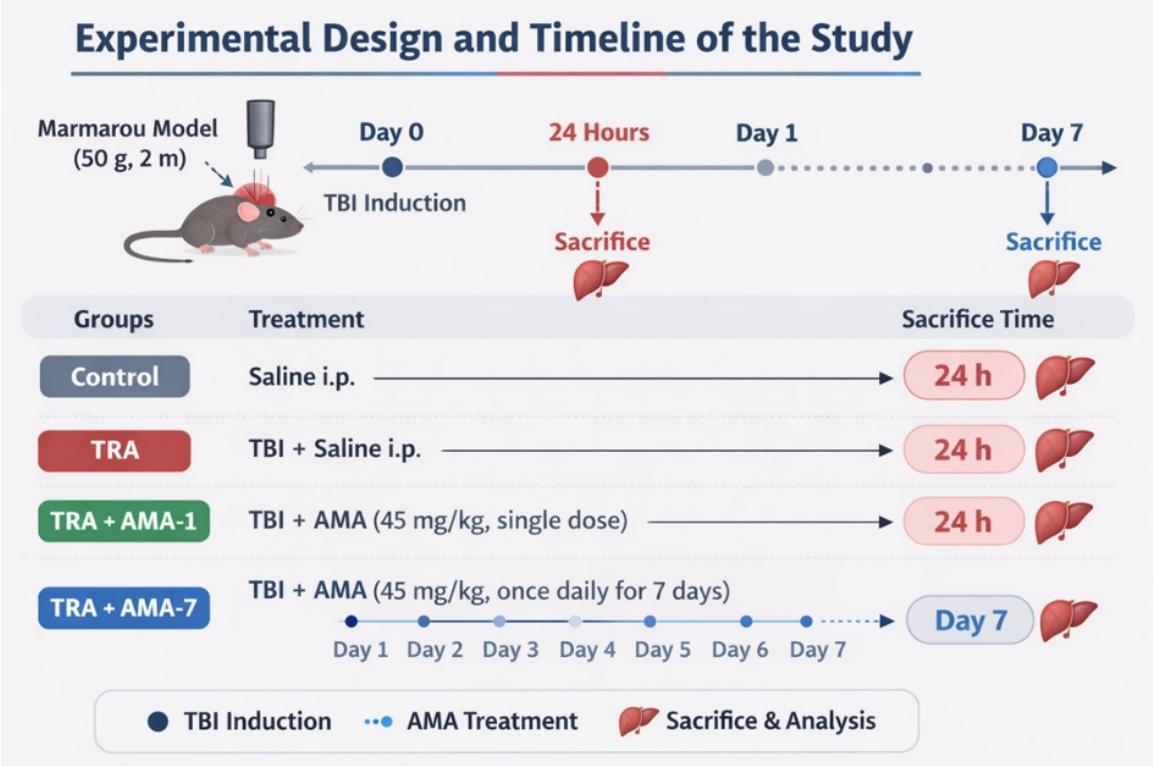



**Figure 1**
The diagram of experimental groups, treatment protocols, and sacrifice time points

fore, the Marmarou model was selected in the present study to investigate hepatic alterations occurring as a secondary consequence of traumatic brain injury. Successful induction of traumatic brain injury was confirmed based on immediate post-impact apnea and transient loss of consciousness observed in all trauma groups.

**Anesthesia and Sacrifice Procedure**

All surgical procedures were performed under anesthesia with Ketamine hydrochloride (Ketalar®, Pfizer, USA) (90 mg/kg) and xylazine (Rompun®, Bayer, Germany) (8–10 mg/kg) administered i.p. Six hours following the final AMA injection, animals were anesthetized and then sacrificed via surgical exsanguination through the inferior vena cava. Liver tissues were rapidly harvested for histopathological and immunohistochemical evaluations.

**Histopathological Method**

Liver tissues from all animals in each experimental group (n = 10 per group) were included in the histopathological evaluation. During necropsy, liver tissue was excised and immediately immersed in 10 % neutral-buffered formalin. After routine dehydration and clearing in a fully automated tissue processor (ASP300S; Leica, Wetzlar, Germany), the specimens were embedded in paraffin. Histopathological and immunohistochemical evaluations were performed by a pathologist blinded to the experimental groups. Serial 5-µm sections were cut on an automated rotary microtome (RM2155; Leica Microsystems, Wetzlar, Germany), stained with hematoxylin–eosin, mounted, and examined by light microscopy. Histopathological alterations were graded according to the modified criteria of Veteläinen et al. (2006) (27). This semi-quantitative scoring system allows evaluation of key histopathological features such as inflammation, hemorrhage, and necrosis, which are relevant indicators of hepatic injury in experimental models, as detailed in Table 1.

**Immunohistochemical Examination**

For immunohistochemical analysis, three series of slices were cut from the paraffin blocks and mounted on slides coated with poly-L-lysine. Serial 5-µm liver sections were placed on poly-L-lysine slides and processed with an avidin–biotin complex protocol to visualise antigen expression. All primary antibodies (dilution 1: 100) were sourced from Abcam®, Cambridge, UK. Immunohistochemistry was performed on the sections using streptavidin-alkaline phosphatase conjugate and a biotinylated secondary antibody after

**Table 1** Histopathology score of hepatic lesions

| Histological criteria | Severity | Description | Score |
|---|---|---|---|
| Hemorrhage | Absent | | 0 |
| | Mild | < 3 foci | 1 |
| | Marked | 4-6 foci | 2 |
| | Severe | > 7 foci | 3 |
| Inflammation | None | | 0 |
| | Moderate | Scattered | 1 |
| | Marked | Foci | 2 |
| | Severe | Diffuse | 3 |
| Necrosis | Absent | 0% | 0 |
| | Mild | <10% | 1 |
| | Marked | 10–50% | 2 |
| | Severe | >50% | 3 |

a 60-minute incubation with the primary antibodies. The Mouse and Rabbit Specific HRP/DAB IHC Detection Kit - Micro-polymer (ab236466) from Abcam (Cambridge, UK) was used as the secondary antibody, and diaminobenzidine (DAB) was employed as the chromogen. For negative controls, the antigen dilution solution was applied instead of primary antibodies. Each evaluation was conducted on blinded samples by a specialized pathologist from another university.

For each marker, the percentage of positively immunostained cells was calculated in ten randomly selected fields per slide from all groups, using an objective magnification of ×40. For each experimental group, liver sections from all animals (n = 10 per group) were analyzed. Microphotographs were captured using the Database Manual CellSens Life Science Imaging Software System (Olympus Corporation, Tokyo, Japan). Quantification of positive staining was carried out in ImageJ v1.48 (version 1.48, National Institutes of Health, Bethesda, MD, USA). An Olympus CX41 model microscope was used for photographing the results, and the Database Manual Cell Sens Life Science Imaging Software System was used for microphotography.

### Statistical Analysis

Statistical analyses were performed using GraphPad Prism software (version 9.0; GraphPad Software Inc., San Diego, CA, USA). Data normality was assessed using the Shapiro–Wilk test. As the data followed a normal distribution, group comparisons were performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Data are presented as mean ± standard deviation (SD), and a p-value < 0.05 was considered statistically significant. Homogeneity of variance was assessed using Levene's test before ANOVA.

## Results

### Histopathological Findings

Histopathological examination of liver tissues revealed marked alterations in the TRA group compared with the control group. Semiquantitative scoring demonstrated significantly higher levels of hyperemia, hemorrhage, inflammation, and necrosis in the TRA group (Figure 2).

Treatment with amantadine reduced the severity of these histopathological alterations. Both the TRA + AMA-1 and TRA + AMA-7 groups showed lower histopathological scores compared with the TRA group.

Among the treatment groups, the TRA + AMA-7 group demonstrated the lowest histopathological injury scores, indicating a greater reduction in hepatic injury following prolonged amantadine administration (Figure 2).

The TRA group demonstrated significantly higher

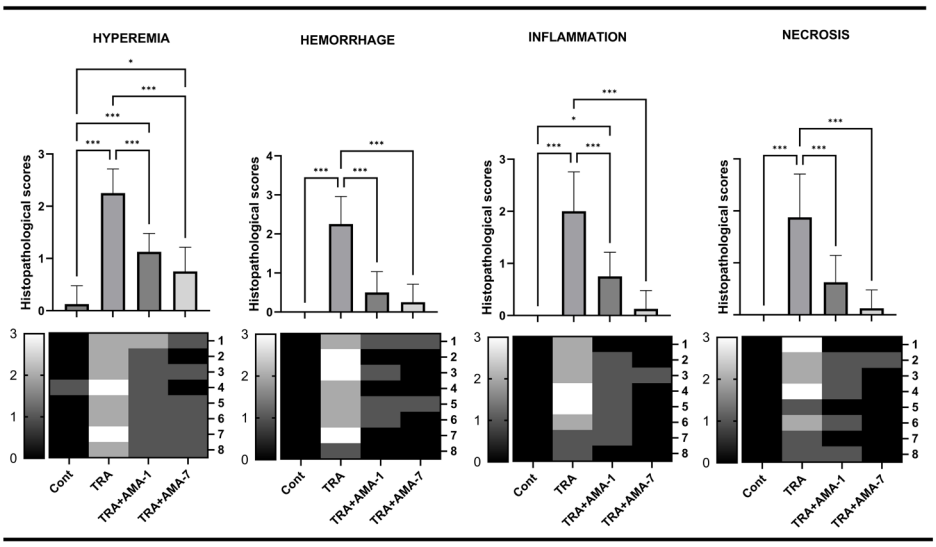



**Figure 2**
**Quantitative histopathological scores of liver tissue in all experimental groups**

Bar graphs and corresponding heatmaps show semiquantitative scoring of hyperemia, hemorrhage, inflammation, and necrosis in liver sections. Values are presented as mean ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test.

histopathological scores compared with the control group ($p = 0.003$). Treatment with amantadine resulted in a significant reduction in hepatic injury scores in both TRA+AMA-1 ($p = 0.021$) and TRA+AMA-7 ($p = 0.0008$) groups compared to the TRA group. Furthermore, a statistically significant difference was observed between the TRA+AMA-1 and TRA+AMA-7 groups ($p = 0.038$), indicating a time-dependent therapeutic effect.

Semiquantitative scoring based on modified Veteläinen criteria showed significant reductions in inflammation, necrosis, and hemorrhage in AMA-treated groups ($p < 0.05$)

**Immunohistochemical Findings**

Immunohistochemical analysis corroborated the histopathological results by demonstrating significant changes in the expression levels of inflammatory markers. In the Cont group, the immunoreactivity of IFN-β, TNF-α, and IL-6 was minimal or absent, as expected in a non-injured physiological state. However, in the TRA group, there was a marked increase in the expression of all three cytokines, predominantly within hepatocytes, but also involving bile duct epithelial cells and inflammatory infiltrates.

Treatment with AMA substantially reduced the immunohistochemical expression of IFN-β, TNF-α, and IL-6 in the liver. The TRA-AMA-1 group exhibited a moderate decrease in marker expression, suggesting early suppression of inflammatory signaling pathways. Notably, the TRA-AMA-7 group demonstrated minimal immunoreactivity, nearly resembling the sham group, reflecting a time-dependent therapeutic effect of AMA in mitigating hepatic inflammation. Positive immunostaining was defined as brown cytoplasmic staining observed in hepatocytes following DAB chromogen development. (Figures 3-5).

Quantitative analysis revealed that cytokine expression levels were significantly higher in the TRA group compared with the control group ($p < 0.001$). Amantadine treatment significantly reduced cytokine expression in both TRA+AMA-1 and TRA+AMA-7 groups compared with the TRA group ($p < 0.05$). Additionally, cytokine levels were significantly lower in the TRA+AMA-7 group compared with the TRA+AMA-1 group ($p = 0.038$), supporting a time-dependent anti-inflammatory effect.

Collectively, the histopathological and immunohistochemical findings indicate that amantadine treatment was associated with reduced liver injury following traumatic brain injury. Both treatment groups demonstrated lower levels of histopathological damage and

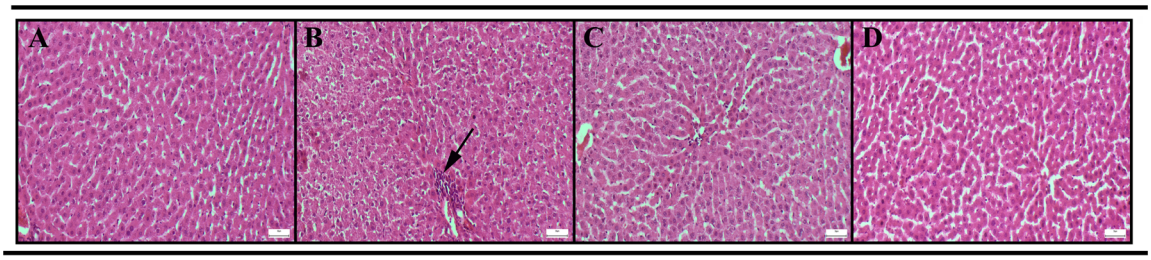



**Figure 3**
**Representative hematoxylin and eosin (H&E) stained liver sections from experimental groups (magnification ×400).**

(A) Cont group: Liver tissue demonstrates normal hepatic architecture with well-preserved hepatocyte cords and sinusoidal spaces, without signs of inflammation, hemorrhage, or necrosis.

(B) TRA group: Disrupted hepatic architecture is observed, with evident sinusoidal dilatation, scattered necrotic foci, and inflammatory cell infiltration (black arrow).

(C) TRA + AMA-1 group: Partial restoration of tissue organization is seen, with reduced necrosis and less inflammatory infiltration compared to the trauma group.

(D) TRA + AMA-7 group: Near-normal liver histology with preserved lobular structure and minimal pathological changes, indicating effective histological protection. Scale bar = 20 μm.

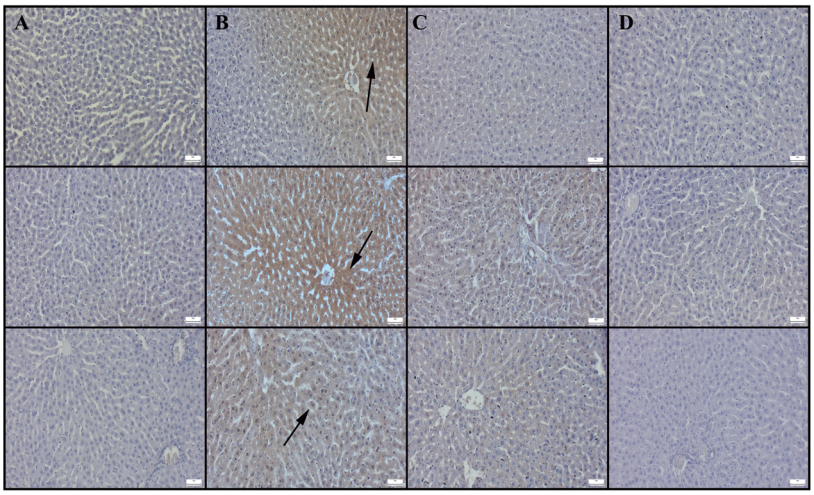



**Figure 4**
**Representative immunohistochemical staining of IFN-β (top row), IL-6 (middle row), and TNF-α (bottom row) in liver sections (×400 magnification).**

(A) Sham group: Minimal or no immunoreactivity for all three markers.

(B) Trauma group: Strong positive staining in hepatocytes, particularly around portal triads and centrilobular areas (black arrows), indicating intense inflammatory activation.

(C) Trauma + AMA (1-day): Moderately decreased immunostaining intensity, with reduced cytokine localization.

(D) Trauma + AMA (7-day): Near-baseline immunoreactivity levels, suggesting marked inhibition of cytokine production. Scale bar = 20 μm for all panels.

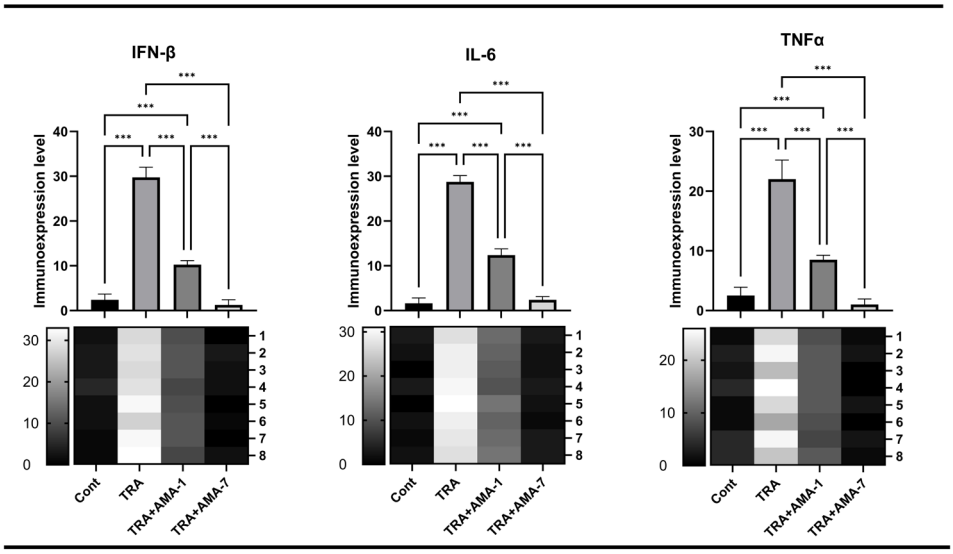



**Figure 5**
**Immunohistochemical expression levels of IFN-β, IL-6, and TNF-α in liver tissue.**

Bar graphs and corresponding heatmaps illustrate the immunoexpression levels of IFN-β, IL-6, and TNF-α in hepatocytes. Data are expressed as mean ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test.

inflammatory marker expression compared with the untreated trauma group. In addition, the TRA + AMA-7 group showed a greater reduction in these alterations compared with the TRA + AMA-1 group, suggesting a potential benefit of prolonged treatment duration. A statistically significant difference was also observed between the TRA+AMA-1 and TRA+AMA-7 groups ($p = 0.038$), supporting a time-dependent therapeutic effect of amantadine.

Overall, these findings suggest that AMA treatment was associated with reduced histopathological liver injury following traumatic brain injury.

## Discussion

The present findings should be interpreted in the context of the growing body of literature investigating systemic inflammatory responses following traumatic brain injury. Traumatic brain injury (TBI) is increasingly recognized as a systemic disorder that extends beyond the central nervous system and affects multiple peripheral organs through inflammatory and neuroendocrine mechanisms. Previous studies have demonstrated that TBI can trigger widespread inflammatory responses characterized by the release of pro-inflammatory cytokines and systemic immune activation (1–4). These processes may contribute to secondary organ dysfunction, including hepatic injury. In the present study, TBI was associated with marked histopathological alterations in liver tissue, including hyperemia, inflammatory infiltration, necrosis, and hemorrhage. These findings are consistent with previous reports showing that brain injury can induce systemic inflammatory responses that negatively affect liver structure and function (4, 18).

The histopathological findings observed in the trauma group are in agreement with earlier experimental studies reporting that systemic inflammatory responses following TBI may disrupt hepatic microcirculation and promote hepatocellular injury (3, 4, 18). In the present study, treatment with amantadine was associated with a reduction in the severity of these histopathological alterations. Both treatment groups demonstrated lower levels of hyperemia, necrosis, inflammation, and hemorrhage compared with the untreated trauma group. These findings suggest that amantadine administration may mitigate some of the secondary inflammatory consequences of traumatic brain injury.

The immunohistochemical findings further supported these observations. Increased immunoreactivity of pro-inflammatory cytokines, including IFN-β, TNF-α, and IL-6, was observed in the trauma group, whereas reduced cytokine expression was detected in animals

treated with amantadine. The role of these cytokines in mediating inflammatory responses following brain injury has been widely documented. Experimental and clinical studies have shown that elevated levels of TNF-α and IL-6 contribute to the development of systemic inflammatory responses and organ injury after TBI (3, 5, 23). In addition, previous research has demonstrated that increased expression of pro-inflammatory cytokines within hepatic tissue is closely associated with hepatocellular damage and inflammatory progression (19–21).

Amantadine has traditionally been used in clinical practice for neurological conditions such as Parkinson's disease and disorders of consciousness after traumatic brain injury (7–9). Beyond its dopaminergic activity, emerging evidence suggests that amantadine may also exhibit anti-inflammatory and neuroprotective properties. Experimental studies have shown that amantadine administration can reduce the expression of pro-inflammatory cytokines and modulate immune responses in different models of neural injury (15, 16). Moreover, studies investigating adamantane derivatives have reported that these compounds may suppress neuroinflammatory signaling pathways and attenuate inflammatory mediator release (17). The reduction in cytokine immunoreactivity observed in the present study is consistent with these previously reported anti-inflammatory effects.

An additional finding of the present study was the difference observed between the short-term and prolonged treatment groups. Animals receiving seven days of amantadine treatment demonstrated lower histopathological injury scores compared with those receiving a single-day treatment protocol. Although the present study was not designed to evaluate pharmacodynamic mechanisms in detail, this observation suggests that treatment duration may influence the degree of histopathological recovery following TBI-related systemic injury.

The systemic inflammatory cascade triggered by traumatic brain injury is known to involve multiple molecular pathways, including cytokine signaling, oxidative stress, and inflammasome activation. Disruption of the blood–brain barrier following TBI may facilitate the release of inflammatory mediators into the systemic circulation, thereby contributing to secondary organ injury (22, 23). In the liver, Kupffer cells play a critical role in responding to circulating inflammatory signals, which may amplify hepatic inflammation and tissue damage. Experimental studies have also implicated inflammasome complexes, particularly the NLRP3 inflammasome, in mediating inflammatory responses following traumatic brain injury (25). These mechanisms may contribute to the hepatic alterations observed after TBI, although the present study did not directly investigate these molecular pathways.

Several limitations of the present study should be acknowledged. First, the study primarily relied on histopathological and immunohistochemical analyses, and functional biochemical markers of liver injury, such as serum ALT or AST levels, were not evaluated. Second, although reduced cytokine immunoreactivity was observed following amantadine treatment, the specific molecular mechanisms underlying this effect were not investigated. Future experimental studies incorporating molecular analyses and biochemical parameters may help clarify the pathways through which amantadine influences systemic inflammatory responses after traumatic brain injury.

In conclusion, the findings of the present study suggest that amantadine treatment was associated with reduced histopathological liver injury following experimental traumatic brain injury in rats. These results support the hypothesis that pharmacological modulation of inflammatory responses may influence secondary organ injury after TBI. Further experimental and clinical investigations are required to better understand the potential therapeutic role of amantadine in mitigating systemic complications of traumatic brain injury.

**Conflict of Interest Statement**
The corresponding author and the co-authors declare that they have no conflicts of interest related to this study.

**Ethical Approval**
All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Ethical approval for the study was obtained from the Suleyman Demirel University Local Animal Experiments Ethics Committee (Approval No: 15.05.2025/514-05).

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**Availability of Data and Materials**
Data available on request from the authors.

**Artificial Intelligence Statement**
During the preparation of this work the authors used ChatGPT-4o to improve language and readability. Af-

ter using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

**Authors Contributions**

ASO: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing-original draft; Writing- review & editing.

MC: Methodology; Validation; Visualization; Writing-original draft, Writing- review & editing.

FCO: Methodology; Validation; Visualization; Writing-original draft, Writing- review & editing.

HA: Conceptualization; Methodology; Validation; Visualization; Writing-original draft; Writing- review & editing

**Editorial**

FCO, one of the co-authors and a member of the MED J SDU sectional editorial board, played no role in the publication process under any name.

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