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Therapeutic Effects of Alpha-Lipoic Acid on High-Dose Ibuprofen-Induced Renal Damage in Rats

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ABSTRACT

Objectives: Nonsteroidal anti-inflammatory drugs, particularly ibuprofen, are commonly used worldwide and can cause nephrotoxicity through prostaglandin inhibition, oxidative stress, and inflammatory activation. This study aimed to investigate the histopathological, fibrotic, and oxidative effects of high-dose ibuprofen administration and to evaluate the therapeutic potential of alpha-lipoic acid) in reversing these changes.

Methods: Twenty-eight male Wistar albino rats were randomly divided into four groups (n=7): Control, Alpha-lipoic acid (100 mg/kg), Ibuprofen (250 mg/kg), and Ibuprofen+Alpha-lipoic acid. Ibuprofen was administered orally for 21 days, while alpha-lipoic acid was given during the last 7 days. Histopathological changes were evaluated using Hematoxylin & Eosin, Masson's Trichrome, and Periodic Acid–Schiff staining. Fibrotic and inflammatory markers (TGF-β1, α-SMA, TLR-4) were assessed immunohistochemically. Oxidative stress was evaluated by measuring malondialdehyde levels and superoxide dismutase activity.

Results: Ibuprofen administration resulted in significant tubular degeneration, hydropic changes, necrosis, tubular dilatation, and hyperemia. Masson's Trichrome staining showed a significant increase in collagen deposition, while Periodic Acid-Schiff staining revealed glomerular and tubular basement membrane thickening. Immunohistochemistry demonstrated marked upregulation of TGF-β1, α-SMA, and TLR-4 ($P<0.001$). Biochemically, malondialdehyde levels were significantly increased ($P<0.01$) and superoxide dismutase activity was markedly decreased ($P<0.001$) compared to controls. Alpha-lipoic acid treatment significantly ameliorated these changes, reducing fibrosis and inflammatory marker expression and restoring malondialdehyde and superoxide dismutase levels toward normal ($P<0.05$).

Conclusions: Alpha-lipoic acid exerts renoprotective effects against ibuprofen-induced nephrotoxicity by reducing oxidative stress, modulating fibrotic pathways, and improving renal histoarchitecture, suggesting its potential as a therapeutic agent in drug-induced kidney injury.

Keywords: Ibuprofen, Alpha-Lipoic Acid, Nephrotoxicity, Renal Fibrosis, Oxidative Stress

Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly over-the-counter agents such as ibuprofen (IBU), are widely used worldwide. This high level of consumption increases the absolute number of adverse drug events (ADEs) associated with NSAIDs in the general population [1, 2]. Although the nephrotoxicity of NSAIDs is generally considered to have a low

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incidence, repeated exposure and high-dose administration can significantly contribute to kidney injury. NSAIDs reduce renal perfusion by inhibiting prostaglandin synthesis, leading to tubular ischemic injury, inflammation, and mitochondrial dysfunction; additionally, they increase oxidative stress at the tissue level, thereby promoting interstitial fibrosis [2–4]. An important factor underlying the kidney's organ-level susceptibility is its high perfusion: the kidneys receive approximately 20–25% of cardiac output, and this high blood flow facilitates the delivery of toxic agents to the tissue and enhances their metabolic effects, making the kidneys particularly vulnerable to drug-induced toxicity [5].

According to data from the Thai Food and Drug Administration (FDA)/ Health Product Vigilance Center (HPVC), drugs used for musculoskeletal disorders account for approximately 14% of reported adverse drug events (ADEs), with IBU and diclofenac among the top 15 drugs most frequently associated with ADEs. This highlights the widespread use of NSAIDs and their potential toxicity profile on a global scale [6]. The primary mechanism underlying NSAID-induced kidney injury involves COX-1 and COX-2 inhibition, leading to reduced prostaglandin production; this can result in renal vasoconstriction, acute kidney injury, and chronic fibrosis [7–10]. Transforming growth factor (TGF)-β1 signaling plays a central role in fibrogenesis by promoting fibroblast and myofibroblast activation, thereby enhancing extracellular matrix production and fibrosis [9, 10]. Furthermore, NSAID exposure increases reactive oxygen species (ROS) generation, elevating oxidative stress and facilitating cellular necrosis/apoptosis [11].

Alpha-lipoic acid (ALA) is a potent antioxidant that is soluble in both water and lipids; it supports cellular homeostasis through multiple mechanisms, including scavenging free radicals, reactivating endogenous antioxidants, chelating metal ions, and modulating inflammation [12, 13]. Exposure to agents such as IBU, which can induce kidney toxicity, increases oxidative damage, leading to interstitial fibrosis and functional impairment. ALA can protect renal function by reducing oxidative stress and inflammation in kidney tissue and by inhibiting TGF-β1 signaling, thereby preventing interstitial fibrosis [14, 15].

In conclusion, the multifaceted effects of ALA reducing oxidative stress, modulating inflammatory responses, and preventing fibrosis position it as a promising therapeutic agent for the prevention and treatment of kidney toxicity. This study aims to evaluate the histopathological, fibrotic, and oxidative effects of high-dose IBU on the kidney and to investigate the potential of ALA to prevent or reverse this damage.

METHODS

Ethics Approval and Experimental Procedures

All experimental procedures were carried out following the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments). Ethics approval was obtained from the Kırşehir Ahi Evran University Local Ethics Committee for Animal Experiments (decision no: 08/04, dated 24.04.2025).

Experimental Groups and Treatment Protocols

A total of 28 male Wistar albino rats, aged between 12 and 14 weeks, were included in the study. The animals were housed under controlled conditions at 25°C with a 12-hour light/dark cycle, provided with unrestricted access to water, and fed a standard laboratory diet at the Experimental and Clinical Research Center of Kırşehir Ahi Evran University, Kırşehir, Turkey.

The rats were randomly assigned into four experimental groups, with seven animals per group (n=7).

Control (C): Rats received 300 µL of corn oil orally for the last 7 days.

Alpha-lipoic acid (ALA): Rats were administered 100 mg/kg of alpha-lipoic acid (Sigma-Aldrich, Cas:1077-28-7, St. Louis, MO, USA) dissolved in 300 µL of corn oil via oral gavage during the last 7 days. [16]

Ibuprofen (IBU): Rats were given 250 mg/kg of ibuprofen (Brufen 400 mg, Turkey) orally via gavage for 21 consecutive days. [17].

Ibuprofen + Alpha-lipoic acid (IBU + ALA): Rats received 250 mg/kg of ibuprofen orally via gavage for 21 days, and during the last 7 days, 100 mg/kg of alpha-lipoic acid dissolved in 300 µL of corn oil was administered via oral gavage.

All procedures were performed at the same time of day to maintain consistency in experimental

conditions. On day 22, tissue samples were collected under general anesthesia, and the animals were euthanized (Figure 1).

Surgical Procedure

On the 22nd day of the experiment, all animals were anesthetized via intraperitoneal injection with ketamine hydrochloride (60 mg/kg) and xylazine hydrochloride (10 mg/kg, 2% solution). Under sterile conditions, a midline laparotomy was performed. Following the incision of the subcutaneous tissue and abdominal muscles, the left kidney was carefully excised. This kidney was fixed in formaldehyde for subsequent histopathological and immunohistochemical analyses. The right kidney was harvested, placed in Eppendorf tubes for biochemical assays, and stored at -80°C until further use

Histopathological Analysis

To histologically assess renal alterations in each experimental group, tissue samples collected at the end of the study were fixed in 10% formaldehyde. Following 72 hours of fixation, the tissues were rinsed under running water, dehydrated through a graded series of alcohols, cleared in xylene, and embedded in paraffin. Sections of 5 µm thickness were cut from the paraffin blocks and mounted onto slides (Leica, Autocut, 14051956472, Germany).

The slides were deparaffinized with xylene, rehydrated through a descending alcohol series (100%, 96%, 80%, 70%, 50%), and washed in water according to standard histological procedures. For general histological evaluation, sections were stained with Hematoxylin and Eosin (H&E) (Bio-Optica 05-06004/L Harris' Hematoxylin & Bio-Optica 05-10002/L Eosin Y 1%) and Periodic Acid-Schiff (PAS) (Best Lab, Turkey). After staining, the sections were dehydrated through an ascending alcohol series, cleared with xylene, and mounted with coverslips using Entellan. Histological examination was performed under a light microscope.

Renal Histopathological Scoring Method

Degenerative changes in the tubular and intertubular areas were assessed semi-quantitatively. In each kidney section, 10 different fields were

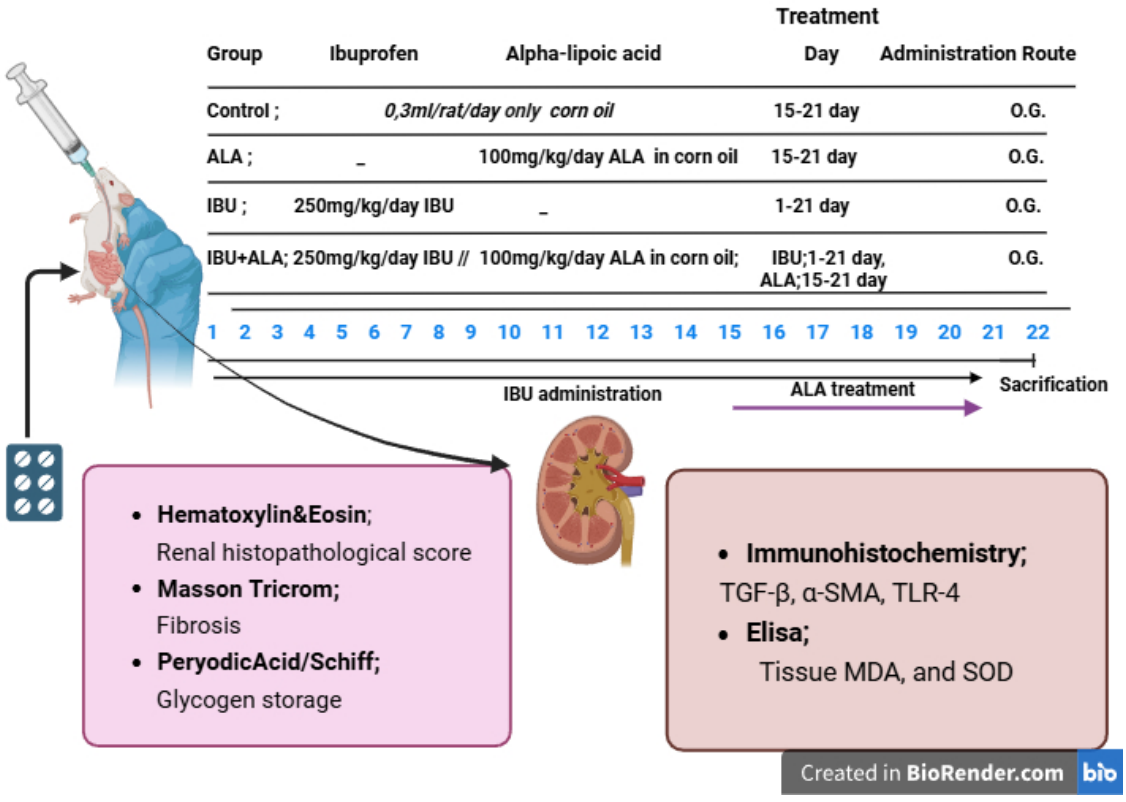

FIGURE 1. Schematic representation of the experimental design.

evaluated for each damage parameter, and average percentage values within each group were calculated. Histopathological changes were scored as follows: changes observed in less than 25% of tubular epithelial cells were scored as 1 (mild), 25–50% as 2 (moderate), 50–75% as 3 (severe), and 75–100% as 4 (very severe) (absence=0, mild=1, moderate=2, severe=3, very severe=4) [18].

Immunohistochemical Analysis

Immunohistochemical staining was performed using the Lab Vision™ UltraVision™ Large Volume Detection System (anti-polyvalent, HRP, TA-125-HL) in combination with the streptavidin-biotin-peroxidase method to assess TGF-β1, α-smooth muscle actin (α-SMA), and Toll-like receptor (TLR)-4 expression in kidney tissues. Five-micrometer sections from paraffin-embedded blocks were deparaffinized, rehydrated, and subjected to antigen retrieval in 5% citrate buffer (microwave, 600 W, 5 min). Endogenous peroxidase activity was blocked with 3% hydrogen peroxide (H_2O_2) for 20 min, and non-specific binding was prevented using blocking serum (room temperature, 10 min). Sections were incubated overnight at 4°C with primary antibodies: TGF-β1 (Proteintech, Cat. No. 21898-1-AP, 1:250), α-SMA (Proteintech, Cat. No. 80008-1-RR, 1:2500), and TLR4 (Proteintech, Cat. No. 19811-1-AP, 1:400). After washing, a biotinylated secondary antibody and streptavidin-peroxidase (Thermo Scientific, SHRP248-B) were applied, followed by DAB development (Lab Vision, TA-125-HL). The sections were counterstained with Mayer's hematoxylin, dehydrated through ascending alcohols, cleared in xylene, and mounted with Entellan. Images were captured from 20 fields under a light microscope, and immunoreactivity was quantified using ImageJ software (NIH, Washington, USA). [19]

Detecting oxidative stress indicators

Kidney tissues collected from all animals were stored at −80 °C. Prior to analysis, the tissues were homogenized and centrifuged, and the resulting supernatants were transferred to Eppendorf tubes for further use. Malondialdehyde (MDA; ELK-BIO, Catalog No: ELK10920) levels and superoxide dismutase (SOD; ELK-BIO, Catalog No: ELK8178) activity were measured using commercial ELISA kits according to the manufacturer's instructions. Optical densities were read using an ELISA reader (ELK808, BIOTEK), and the results were expressed as nmol/mg protein.

Statistical Analysis

The results obtained from the analyses were evaluated using the GraphPad Prism 9.0 statistical software. The Shapiro-Wilk test was performed to assess the normality of data distribution. For comparisons involving multiple groups, one-way analysis of variance (ANOVA) and the Kruskal-Wallis test were used. Post hoc analyses were conducted using the Bonferroni test following ANOVA and the Dunn test following the Kruskal-Wallis test, both of which identified significant differences between variables. A P-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

Alpha-Lipoic Acid Effectively Reduces Ibuprofen-Induced Renal Damage

In the renal tissues of the C and ALA groups, the glomeruli, cortex, and medullary tubules exhibited normal histological architecture. In the group administered IBU at a dose of 250 mg/kg for 21 days to induce nephrotoxicity, degenerative changes in the tubular epithelium, hydropic degeneration, necrotic tubular epithelial cells, tubular dilatation, and marked hyperemia in the intertubular and glomerular regions were observed. In the group treated with ALA during the last 7 days of IBU administration IBU+ALA, when compared with both the control and IBU groups, a marked reduction in tissue damage was detected. Restoration of normal histological architecture was observed in the stromal and parenchymal regions, with only a limited number of degenerative cells remaining (Figure 2).

In MT staining, increased collagen fiber density was observed as blue/purple areas in the IBU group, whereas this increase was milder in the IBU+ALA group. PAS staining revealed prominent thickening of glomerular and tubular basement membranes, along with intense staining and glycogen accumulation in the tubular epithelium in the IBU group. In contrast,

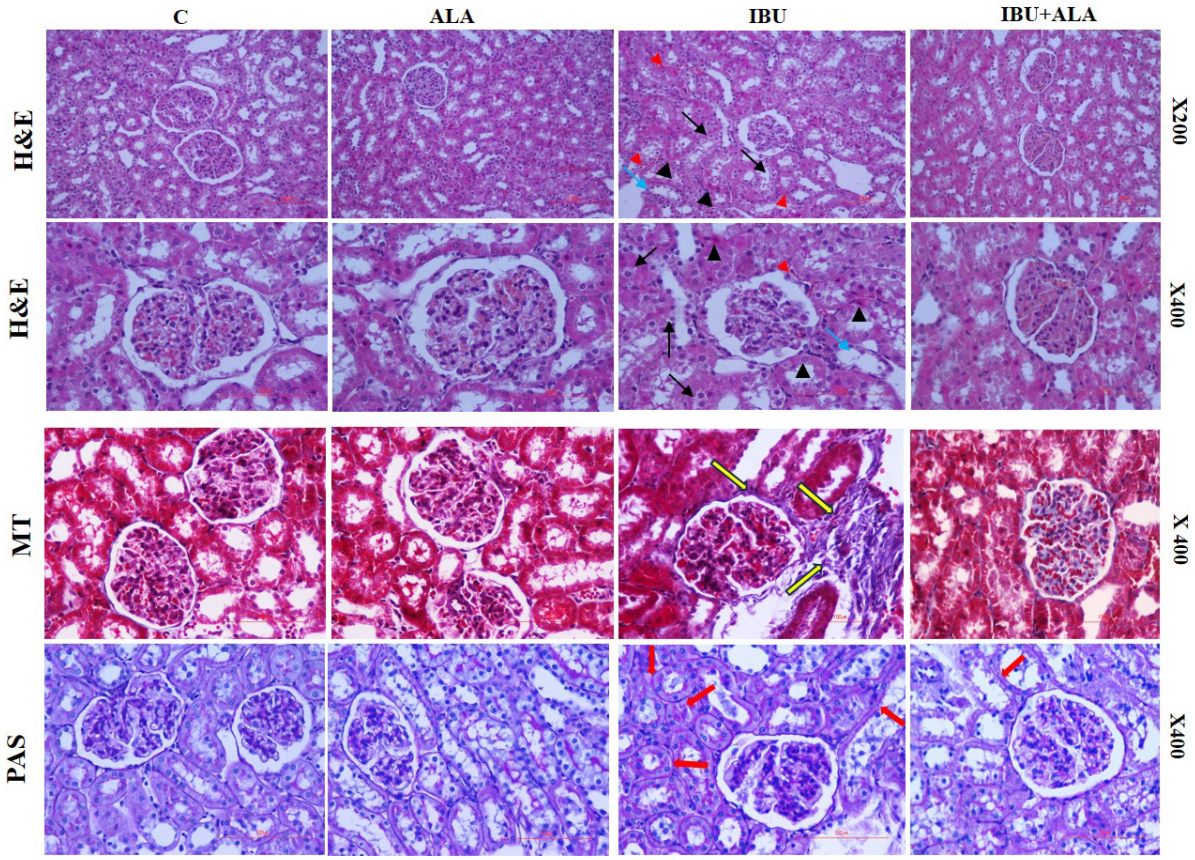

FIGURE 2. Histological sections of renal tissue (Nikon Eclipse Si, Tokyo, Japan; scale bar: 100 µm). Hematoxylin&Eosin (H&E) stained sections show preserved normal histological architecture of glomeruli, cortex, and medullary tubules in Control (C) and Alpha-lipoic acid (ALA)-only groups. In the Ibuprofen (IBU) group, marked histopathological changes are observed including necrotic tubular epithelial cells (black arrow), hydropic degeneration (black arrowhead), tubular dilatation (blue arrow), and widespread hyperemia in glomerular and intertubular regions (red arrowhead). In the IBU+ALA group, histological abnormalities are significantly reduced compared to the IBU group, with largely preserved tubular and glomerular structures and only limited presence of degenerative cells. Masson's Trichrome (MT) stained sections show intense collagen accumulation (yellow arrow) in the IBU group, which is significantly reduced in the IBU+ALA group. Periodic Acid-Schiff (PAS) staining reveals thickening of tubular and glomerular basement membranes, glycogen accumulation, and structural changes in Bowman's capsule (red arrow) in the IBU group, while these changes are minimal and similar to the control groups in the IBU+ALA group.

basement membrane thickness and glycogen accumulation in the IBU+ALA group were minimal and similar to the control groups (Figure 2).

Histopathological scoring revealed a marked increase in tubular degeneration, necrosis, dilatation, vascular hyperemia, collagen deposition, and glycogen accumulation in the IBU group compared with the C and ALA groups ($P<0.001$). Among these parameters, tubular degeneration and necrosis reached the highest scores, indicating severe IBU-induced nephrotoxicity. In contrast, co-administration of ALA (IBU+ALA group) significantly ameliorated these pathological changes ($P<0.01$), showing a clear reduction in tubular and vascular injury, as well as in collagen and glycogen accumulation. These findings suggest that ALA treatment effectively mitigated IBU-induced renal damage and partially restored normal histological architecture (Figure 3).

Alpha-Lipoic Acid Improves Ibuprofen-Induced Tubulointerstitial Fibrosis

In renal tissues, immunoreactivity of TGF-β1, a key marker of fibrosis, was minimal in C and ALA-only groups, with limited staining in glomerular and

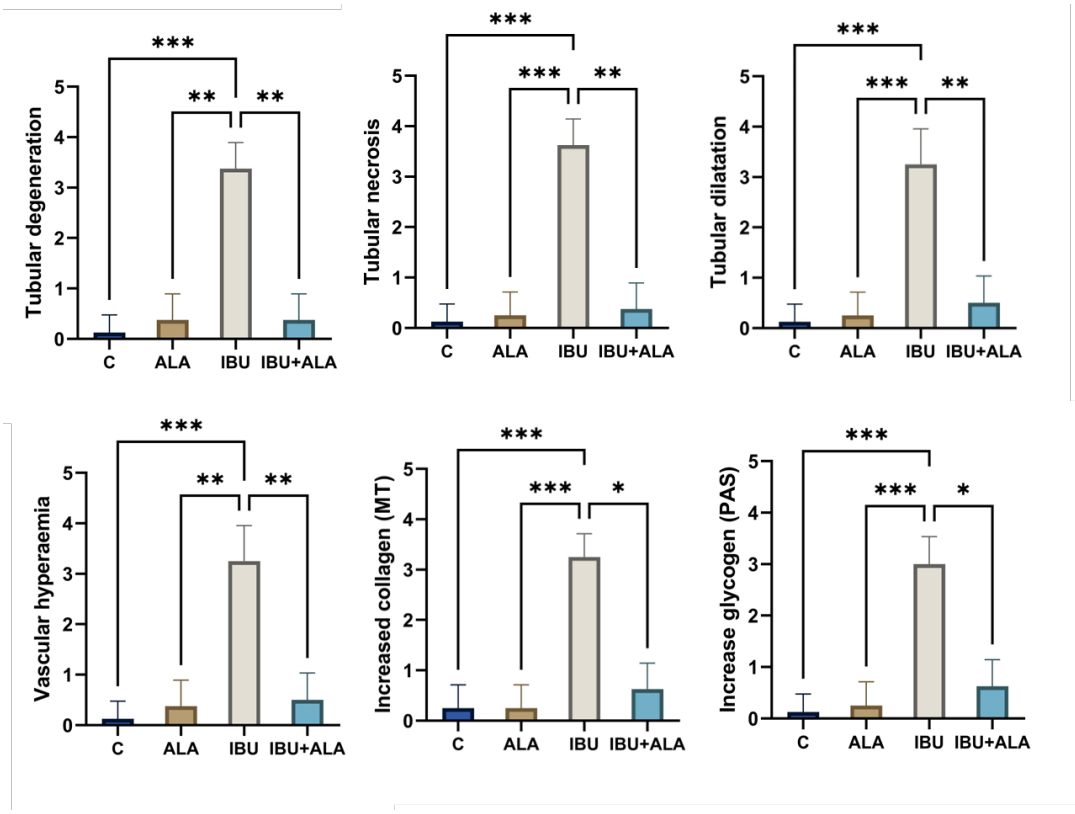

FIGURE 3. Histopathological scoring of renal tissue across experimental groups. Quantitative evaluation of tubular degeneration, tubular necrosis, tubular dilatation, vascular hyperemia, collagen deposition, and glycogen accumulation in Control (C), Alpha-lipoic acid (ALA), Ibuprofen (IBU), and IBU+ALA groups. Data are expressed as mean±standard deviation. *P<0.05, P<0.01, and *P<0.001 indicate statistically significant differences between the groups.

tubular areas. In the IBU group, TGF-β1 expression was significantly increased, particularly showing widespread cytoplasmic staining in the tubulointerstitial area. This increase was markedly reduced in the IBU+ALA group, with staining intensity approaching that of the control groups. Similarly, α-SMA immunoreactivity was very low in control and ALA groups but markedly elevated in glomerular and interstitial regions of the IBU group, indicating myofibroblast activation. ALA treatment significantly decreased α-SMA expression, bringing it close to control levels. TLR-4 expression also significantly increased in the IBU group, with strong cytoplasmic staining in glomerular, tubular, and interstitial areas, while the IBU+ALA group showed reduced and more limited TLR-4 staining. These findings suggest that ALA exerts a protective effect on renal tissue by suppressing IBU-induced fibrotic and inflammatory responses (Figure 4).

TGF-β1 and TLR-4 immunoreactivity remained low in the C and ALA groups but showed a statistically significant increase in the IBU group (P<0.001). This elevation was markedly reduced in the IBU+ALA group, approaching control levels (P<0.001). Similarly, α-SMA immunoreactivity was significantly elevated in the glomerular and interstitial regions of the IBU group (P<0.001); however, ALA treatment markedly suppressed this increase, restoring levels close to those of the controls (P<0.05). These findings indicate that ALA attenuates IBU-induced fibrotic and inflammatory responses, exerting an immunoregulatory effect in renal tissue (Figure 5).

Alpha-Lipoic Acid Reduces Oxidative Stress by Modulating MDA and SOD Levels

MDA, lipid peroxidation marker, was significantly elevated in the IBU group compared to the control (C) and ALA groups (P<0.001), indicating pronounced oxidative stress following IBU exposure. In contrast, MDA levels were significantly reduced in the IBU+ALA group compared to the IBU group (P<0.01), though they did not completely return to

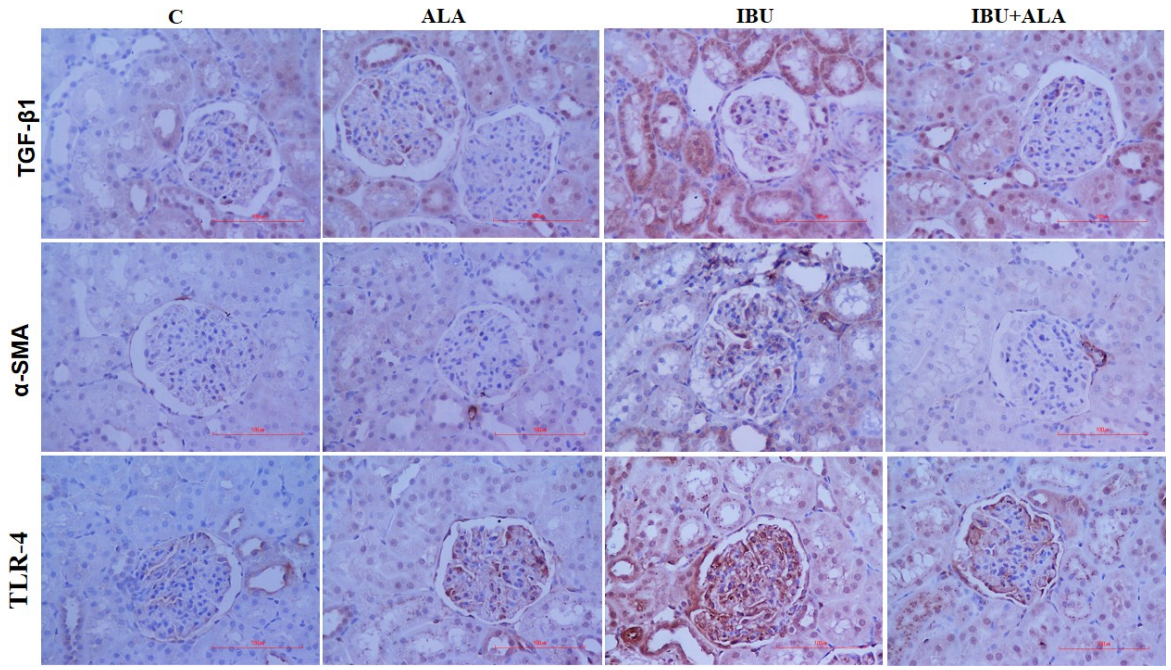

FIGURE 4. Immunohistochemical staining of TGF-β1, α-SMA, and TLR-4 in renal tissues (scale bar: 100 µm, Magnification: 400×). Minimal immunoreactivity was observed in Control (C) and Alpha-lipoic acid (ALA) groups. In the Ibuprofen (IBU) group, expressions of TGF-β1, α-SMA, and TLR-4 were significantly increased, with intense positive staining in tubulointerstitial areas. In the IBU+ALA group, these increases were markedly reduced, showing staining patterns similar to the control group.

control levels. Regarding antioxidant status, SOD activity was highest in the ALA group, showing a significant increase compared to control (P<0.001). IBU administration caused a marked reduction in SOD activity compared to both C and ALA groups (P<0.001), confirming suppression of endogenous antioxidant defenses. However, in the IBU+ALA group, SOD activity was significantly improved compared to the IBU group (P<0.001), approaching levels observed in the control group. These results

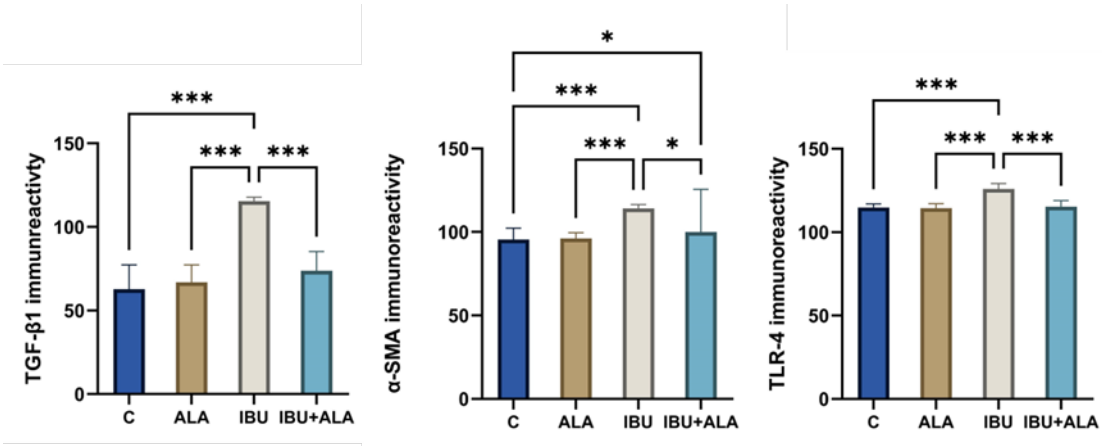

FIGURE 5. Immunohistochemical staining of TGF-β1, α-SMA, and TLR-4 in renal tissues (scale bar: 100 µm, Magnification: Quantitative analysis of TGF-β1, α-SMA, and TLR-4 immunoreactivity in renal tissues. Ibuprofen (IBU) treatment significantly increased the expression of all three markers (*P<0.001), while Alpha-lipoic acid (ALA) co-treatment markedly reduced these elevations, approaching control levels. Data are presented as mean±standard deviation. *P<0.05 and ***P<0.001 indicate statistically significant differences between groups.**

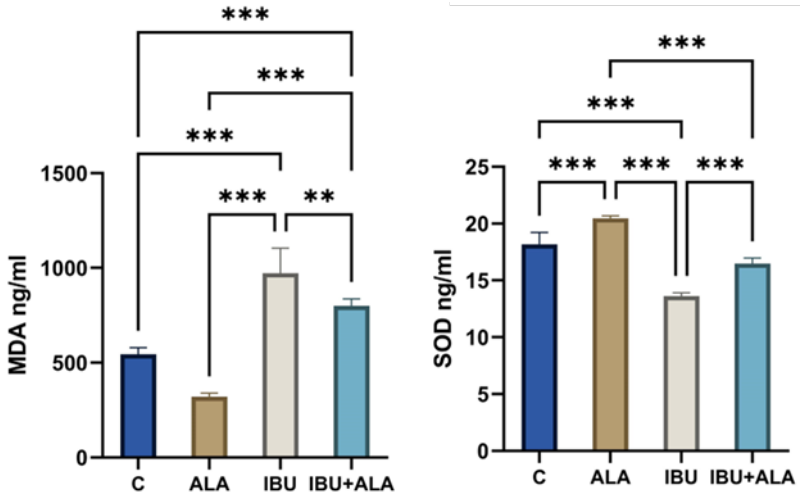

FIGURE 6. Renal tissue oxidative stress parameters. Quantitative analysis of malondialdehyde (MDA) levels and superoxide dismutase (SOD) enzyme activity. Data are presented as mean±standard deviation. **P<0.01, ***P<0.001 indicate statistically significant differences between groups.

collectively suggest that ALA supplementation attenuates IBU-induced oxidative damage by both reducing lipid peroxidation and restoring antioxidant enzyme activity (Figure 6).

DISCUSSION

In the present study, the nephrotoxic potential of high-dose ibuprofen (IBU, 250 mg/kg) and the protective effects of alpha-lipoic acid (ALA, 100 mg/kg) were comprehensively evaluated using histopathological, immunohistochemical, and biochemical approaches. Prolonged IBU exposure caused distinct renal injury characterized by tubular degeneration, necrosis, glomerular and interstitial congestion, and excessive collagen accumulation, accompanied by increased TGF-β1, α-SMA, and TLR-4 expression. These findings indicate that IBU promotes oxidative stress, inflammation, and fibrosis in renal tissue. Co-administration of ALA markedly mitigated these alterations, preserved renal architecture, reduced fibrotic and inflammatory responses, and restored antioxidant balance, as evidenced by lower MDA and higher SOD levels. These findings indicate that ALA exerts renoprotective effects against IBU-induced nephrotoxicity by modulating oxidative stress, inflammation, and fibrogenesis.

Histopathological analyses confirmed the severity of IBU-induced renal injury, showing tubular epithelial degeneration, necrosis, tubular dilatation, and pronounced hyperemia in glomerular and intertubular regions. These alterations align with the classical nephrotoxic profile of NSAIDs, which induce renal hypoperfusion and oxidative stress through prostaglandin depletion [2-5, 20-22]. Conversely, ALA administration preserved the structural organization of the renal parenchyma, markedly reducing necrosis and interstitial disorganization. In Masson's Trichrome staining, collagen accumulation was substantially lower, and basal membrane thickening and glycogen accumulation observed in the PAS staining were restored toward normal morphology. These improvements demonstrate ALA's capacity to maintain renal histoarchitecture and attenuate tissue injury, in agreement with previous studies reporting that ALA preserves renal morphology and reduces collagen accumulation in nephrotoxicity models [14, 23, 24].

The upregulation of TGF-β1 and α-SMA in the IBU group indicates activation of fibrogenic pathways responsible for tubular injury and interstitial remodeling. TGF-β1, a central mediator of renal fibrosis, activates both Smad-dependent and Smad-independent signaling to promote fibroblast-to-myofibroblast differentiation, leading to excessive collagen synthesis and extracellular matrix deposition [25]. α-SMA serves as a hallmark of myofibroblast activation and correlates with extracellular matrix accumulation in renal fibrosis

models such as diabetic kidney disease [26]. The suppression of TGF-β1 and α-SMA expression in the ALA-treated group suggests that ALA mitigates IBU-induced fibrogenesis by modulating the TGF-β1/Smad signaling cascade, consistent with previous evidence demonstrating the antifibrotic potential of ALA in renal injury models [26, 28].

Comprehensive reviews and recent studies have emphasized the renoprotective roles of ALA, including its ability to reduce oxidative stress, suppress inflammation, and modulate fibrogenic pathways; therefore, our finding that ALA partially reversed IBU-induced fibrosis is consistent with the established evidence in the literature [27, 29]. Lipid peroxidation mediated by ROS, reflected by elevated MDA levels, along with a decline in antioxidant defense systems particularly reduced SOD activity is widely recognized as an early indicator of renal injury. For instance, a recent study demonstrated that ALA significantly attenuated oxidative stress in an LPS-induced kidney injury model by reducing MDA and enhancing SOD activity [27]. In our study, IBU administration resulted in a marked increase in MDA levels and a significant decrease in SOD activity, suggesting enhanced lipid peroxidation and impaired endogenous antioxidant defense in renal tissue. These findings are consistent with reports from an iron-overload-induced nephrotoxicity model, where 100 mg/kg ALA treatment significantly reduced MDA levels and restored SOD and other antioxidant enzyme activities [30]. Moreover, in an LPS-induced renal oxidative stress model, ALA administration has been reported to reduce TBARS and other oxidative markers while enhancing antioxidant defense systems such as SOD and total glutathione [27]. Therefore, our findings confirm the capacity of ALA to mitigate ibuprofen-induced oxidative damage and are consistent with the growing body of evidence in the literature.

Strengths and Limitations

The study was conducted using a single animal species and sex, which may restrict generalizability. Moreover, specific intracellular signaling pathways underlying ALA-mediated protection were not directly investigated. The evaluation was limited to a single ALA dose and treatment duration, and functional renal biomarkers were not assessed. Future studies addressing these aspects would further strengthen the translational value of the results.

CONCLUSION

In conclussion, this study demonstrates that high-dose ibuprofen induces significant renal damage characterized by tubular degeneration, interstitial fibrosis, increased TGF-β1, α-SMA, and TLR-4 expression, as well as enhanced oxidative stress, as evidenced by elevated MDA levels and decreased SOD activity. Importantly, alpha-lipoic acid treatment significantly attenuated these changes, restoring renal histoarchitecture, reducing fibrosis and inflammatory marker expression, and improving oxidative balance. These findings highlight the potential of ALA as a therapeutic option for mitigating drug-induced nephrotoxicity and preventing progression toward chronic kidney disease. Future studies should focus on dose optimization and elucidation of the molecular mechanisms underlying its renoprotective effects.

Ethics Approval and Consent to Participate

This study was approved by the Kırşehir Ahi Evran University Animal Experiments Local Ethics Committee (Decision No: 08/4; date: 24.04.2025). All experimental procedures involving animals were conducted in accordance with the ethical standards of the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Data Availability

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Authors' Contribution

Study Conception: HTY; Study Design: HTY; Supervision: HTY; Funding: N/A; Materials: HTY; Data Collection and/or Processing: HTY; Statistical Analysis and/or Data Interpretation: HTY; Literature Review: HTY; Manuscript Preparation: HTY; and Critical Review: HTY.

Conflict of Interest

The author(s) disclosed no conflict of interest during the preparation or publication of this manuscript.

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Generative Artificial Intelligence Statement

The author(s) declare that no artificial intelligence-based tools or applications were used during the preparation process of this manuscript. The all content of the study was produced by the author(s) in accordance with scientific research methods and academic ethical principles.

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