Pharmaceutical Sciences and Drug Design
ISSN: 3062-4428
2025, Volume 5, Page No: 242-257

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Protective Effects of Lactobacillus plantarum KSFY06 Against Oxidative Stress and Inflammation in D-Gal/LPS-Induced Acute Liver Injury in Mice

Carlos Mendes[1]*, Vitor Almeida[1]

[1]Department of Phytochemistry, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal.

***E-mail** ✉ carlos.mendes.pt@outlook.com

Received: 18 August 2025; **Revised:** 22 November 2025; **Accepted:** 25 November 2025

ABSTRACT

This research investigated whether Lactobacillus plantarum KSFY06 (LP-KSFY06) could prevent acute liver damage caused by combined D-galactose and lipopolysaccharide (D-Gal/LPS) exposure in mice. The antioxidant activity of LP-KSFY06 was first examined using in vitro radical scavenging assays. In mice, the effects on liver injury were assessed through organ weight indices, serum liver function markers, oxidative stress parameters, inflammatory cytokines, gene expression levels, and histological examination of liver tissue. LP-KSFY06 demonstrated strong free radical scavenging capacity against DPPH and ABTS in vitro. In vivo, mice pretreated with LP-KSFY06 showed improved liver histology and organ indices, indicating reduced tissue injury. The treatment preserved antioxidant enzyme activities, including SOD, GSH, GSH-Px, CAT, and total antioxidant capacity, and inhibited the elevation of AST, ALT, MDA, MPO, and NO induced by D-Gal/LPS. LP-KSFY06 also shifted the inflammatory balance by increasing the anti-inflammatory cytokine IL-10 and suppressing pro-inflammatory cytokines IL-6, IL-1β, TNF-α, and IFN-γ, consistent with observed changes in gene expression. Mechanistically, LP-KSFY06 downregulated the expression of Keap1, NLRP3, ASC, caspase-1, NF-κB, IL-18, and p38 MAPK, while upregulating Nrf2, HO-1, NQO1, IκB-α, and Trx, suggesting involvement of the Keap1–Nrf2/ARE and NLRP3/NF-κB pathways in its hepatoprotective action. LP-KSFY06 functions as a multifunctional probiotic with strong antioxidant and anti-inflammatory effects, providing effective protection against D-Gal/LPS-induced acute liver injury and supporting liver health in mice.

Keywords: Lactobacillus plantarum KSFY06, D-galactose, Lipopolysaccharide, Acute liver injury, Mice

How to Cite This Article: Mendes C, Almeida V. Protective Effects of Lactobacillus plantarum KSFY06 Against Oxidative Stress and Inflammation in D-Gal/LPS-Induced Acute Liver Injury in Mice. Pharm Sci Drug Des. 2025;5:242-57. https://doi.org/xxxxxxxxxxxxxxxxxx

Introduction

Acute liver injury (ALI) represents a group of liver disorders characterized by massive hepatocyte death. If untreated, ALI can progress to liver failure, which carries a high risk of mortality [1]. Since liver transplantation is currently the only effective treatment for acute liver failure, understanding the mechanisms behind ALI and developing targeted therapies is critical for improving patient outcomes [2, 3].

Oxidative stress occurs when the generation of reactive oxygen species (ROS) exceeds the body's antioxidant capacity [4]. ROS can damage unsaturated fatty acids in cell membranes, triggering lipid peroxidation that produces secondary oxidation products. These products can further affect nucleic acids and proteins, impairing cellular function and causing varying degrees of oxidative damage [5]. Evidence shows that oxidative stress contributes to multiple diseases, including allergies, asthma, Alzheimer's disease, diabetes, hypertension, hyperlipidemia, coronary heart disease, and cancer [6–8].

Several signaling molecules, such as Nrf2, NF-κB, and p38 kinase, are activated in response to oxidative stress. Among these, Nrf2 serves as a key regulator of the cellular antioxidant defense system. Dysregulation or deficiency of Nrf2 enhances oxidative stress-induced cytotoxicity, promoting hepatocyte apoptosis and inflammation, and leading to liver injury. Consequently, the Nrf2 signaling pathway is a crucial target for therapies

against oxidative stress-induced liver damage [9]. The Keap1–Nrf2/ARE pathway, in particular, plays a central role in antioxidant defense, regulating enzymes that neutralize ROS and other harmful compounds [10].

D-galactose (D-Gal) is widely used in animal models to induce liver injury. Excess D-Gal that cannot be metabolized disrupts cellular homeostasis, alters oxidase activity, and increases production of peroxides and oxidative products. This leads to structural and functional damage to biomolecules, triggering systemic inflammatory responses and potentially resulting in acute liver injury and multi-organ dysfunction [11]. Lipopolysaccharide (LPS), released during bacterial growth or cell lysis, activates non-specific immune responses, leading to the production of inflammatory cytokines that can damage key organs including the liver [12]. The combination of D-Gal and LPS is commonly used to mimic ALI in experimental models [13, 14]. D-Gal sensitizes hepatocytes to LPS, increasing lethality, but the detailed mechanisms of liver injury induced by D-Gal/LPS remain incompletely understood [15].

Antioxidants can neutralize free radicals and enhance the activity of endogenous antioxidant enzymes, reducing the accumulation of harmful peroxides such as malondialdehyde (MDA) and lipofuscin (LP), thereby providing protective effects [16]. Lactobacillus species, including L. rhamnosus, L. fermentans, and L. plantarum, have demonstrated antioxidant activity both in vitro and in vivo, scavenging free radicals, inhibiting lipid peroxidation, and chelating metal ions [17–19]. Their effects on oxidative damage are reflected by increased expression of antioxidant genes and decreased peroxide activity in vivo [20].

In this study, a novel Lactobacillus plantarum strain, KSFY06 (LP-KSFY06), was isolated from traditional fermented yoghurt in Kashgar, Xinjiang, China. Using a D-Gal/LPS-induced ALI mouse model, we evaluated the protective effects of LP-KSFY06 in vivo and explored the underlying mechanisms, providing insights for developing functional probiotics to promote liver health.

Materials and Methods

Strain and Reagents

Lactobacillus plantarum KSFY06 (LP-KSFY06) was registered and preserved (preservation number: 15,659) at the China General Microbiological Culture Collection Center (CGMCC, Beijing, China). LPS (from Escherichia coli 055:B5) was purchased from Beijing Solarbio Science & Technology Co., Ltd. (Beijing, China), and D-galactose was obtained from Sinopharma Chemical Reagent Co., Ltd. (Beijing, China).

Animals

Forty male Kunming mice (6–8 weeks old, SPF) were purchased from the Experimental Animal Center of Chongqing Medical University (Chongqing, China). Mice were housed in standard barrier cages at 20–25°C with 50–60% relative humidity under a 12-hour light/dark cycle, with free access to food and water.

Cultivation and administration of LP-KSFY06

Single colonies of LP-KSFY06 were inoculated into MRS liquid medium and incubated at 37°C for 20 h until reaching early stationary phase. Cultures were then transferred (3% v/v inoculation) into fresh MRS medium and incubated for an additional 18 h. Bacteria were collected by centrifugation (4°C, 4000 rpm, 10 min), washed twice with saline, and resuspended to final concentrations of 2.5×10^{9} and 2.5×10^{10} CFU/kg body weight for administration.

In vitro evaluation of antioxidant activity

The antioxidant capacity of LP-KSFY06 was assessed using DPPH and ABTS radical scavenging assays. For the DPPH assay, 0.5 mL of LP-KSFY06 solution at either 2.5×10^{9} CFU/mL (low concentration) or 2.5×10^{10} CFU/mL (high concentration) was mixed with 2 mL of 0.33 mmol/L DPPH solution (Sinopharm Chemical Reagent Co., Ltd., Beijing, China). The mixture was incubated in the dark at room temperature for 30 minutes, and absorbance was read at 517 nm using a BioMate 3S spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Vitamin C (0.2 mg/mL) was used as a reference antioxidant, and each experiment was performed in triplicate [21].

For the ABTS assay, 0.4 mL of LP-KSFY06 solution (same concentrations as above) was combined with 1 mL of prepared ABTS solution and allowed to react in the dark at room temperature for 10 minutes. Absorbance was recorded at 734 nm. The ABTS working solution was prepared by mixing 3 mg ABTS in 0.8 mL water (reagent

A) with 1 mg potassium persulfate in 1.5 mL water (reagent B), combining 0.2 mL of each, incubating in the dark for 12 hours, and diluting with ethanol to reach an OD_{734} of 0.7 ± 0.02. Vitamin C (0.2 mg/mL) served as the positive control, and each test was repeated three times [22].

Induction of acute liver injury in mice

Following a 7-day acclimation, forty male Kunming mice were randomly assigned to four experimental groups (normal, model, low-dose, high-dose), with ten mice per group, to evaluate the protective effects of LP-KSFY06 on D-Gal/LPS-induced liver injury. All animals were provided standard feed and water for four weeks. The control group received no additional treatment. In the model group, acute liver injury was induced by intraperitoneal injection of D-Gal (250 mg/kg body weight) and LPS (25 mg/kg body weight) on the final day of week four.

Mice in the treatment groups were given daily oral doses of LP-KSFY06 from weeks two to four: 10^9 CFU/kg for the low-dose group and 10^{10} CFU/kg for the high-dose group. On the last day, these mice also received the same D-Gal/LPS injections as the model group. For all treatments, the volume of administration was 0.1 mL per 10 g body weight. The experimental design is summarized in **Figure 1.**

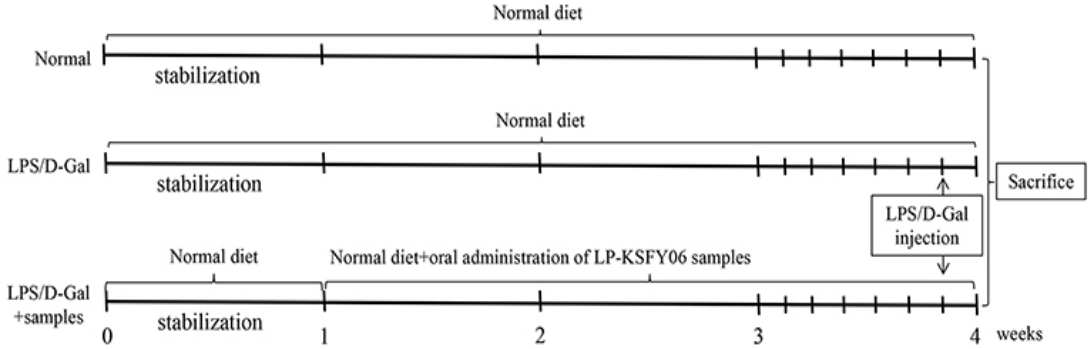

Figure 1. Study Design for D-Gal/LPS-Induced Liver Injury in Kunming Mice

Four experimental groups were established: a normal group with no interventions; a model group that received intraperitoneal injections of D-galactose (250 mg/kg body weight) and LPS (25 mg/kg body weight); a low-dose group, administered LP-KSFY06 orally at 10^9 CFU/kg body weight along with D-Gal/LPS injection; and a high-dose group, which received LP-KSFY06 at 10^{10} CFU/kg body weight plus D-Gal/LPS injection. Each administration, whether oral or intraperitoneal, was given at 0.1 mL per 10 g body weight. The mice were fed a standard diet composed of wheat flour (25%), oatmeal (25%), corn flour (25%), soybean flour (10%), fish meal (8%), hog bone powder (4%), yeast powder (2%), and salt (1%) [23].

Sample collection

Mice were euthanized two hours after the last treatment following an 18-hour fast. Blood was collected for serum separation, and major organs were dissected, weighed, and processed. Sections of tissues were fixed in 10% formalin for histological analysis, while remaining tissues were stored at −80°C for further experiments. The study was approved by the Ethics Committee of Chongqing Collaborative Innovation Center for Functional Food (Approval No. 201904045B) and followed national ethical standards for laboratory animals in China (GB/T 35892–2018) [23].

Histopathological examination

Liver and spleen samples (~0.5 cm^2) were fixed in 10% neutral formalin for 48 hours, then embedded in paraffin and cut into 4 μm sections. H&E staining was performed, and tissue morphology was observed under a BX43 light microscope (Olympus, Tokyo, Japan) [23].

Biochemical analysis of serum and liver

Blood samples were maintained at 4°C for 2 hours and centrifuged at 3000 rpm for 15 minutes at 4°C (BY-80C centrifuge, Beijing Baiyang Medical Instrument Co., Ltd., Beijing, China). The supernatant serum was stored at −80°C. Liver tissue (0.1 g) was homogenized in 0.9 mL saline using a Bioprep-24 homogenizer (Hangzhou

Aosheng Instrument Co., Ltd., Hangzhou, China) with three 30-second cycles at 6 m/s. Commercial kits (Nanjing Jiancheng Institute of Bioengineering, Nanjing, China) were used to quantify AST, ALT, MPO, MDA, NO, T-AOC, CAT, GSH, GSH-Px, and SOD in both serum and liver tissues [23].

Cytokine detection

The concentrations of TNF-α, IFN-γ, IL-1β, IL-6, and IL-10 were measured in serum and liver homogenates using ELISA kits (Abcam, Cambridge, MA, USA) following the manufacturer's instructions [23].

Gene expression analysis by RT-qPCR

Total RNA from liver tissues was extracted using TRIzol™ reagent (Thermo Fisher Scientific) after homogenization with the Bioprep-24 system. RNA was standardized to 1 μg/μL and reverse-transcribed into cDNA. For qPCR, 1 μL of cDNA was combined with 2 μL of forward and reverse primers (10 μM each) and 10 μL of premix. The reaction conditions were: initial denaturation at 95°C for 3 minutes, followed by 40 cycles of 30 seconds at 60°C and 1 minute at 95°C. β-Actin served as the internal control, and relative expression levels were calculated using the 2^−ΔΔCT method. Primer sequences are provided in **Table 1** [23].

Table 1. Sequences of Primers Used for RT-qPCR Analysis

Gene Name	Sequence
SOD1	F: 5′-AACCAGTTGTGTTGTGAGGAC-3’
	R: 5′-CCACCATGTTTCTTAGAGTGAGG-3’
SOD2	F: 5′-CAGACCTGCCTTACGACTATGG-3′
	R: 5′-CTCGGTGGCGTTGAGATTGTT-3′
CAT	F: 5′-GGAGGCGGGAACCCAATAG-3′
	R: 5′-GTGTGCCATCTCGTCAGTGAA-3′
GSH	F: TATCAGAGGCGGGAAATCTCTT-3′
	R: ATTCTTGCTTCGGCCACATAC-3′
GSH-Px	F: 5′-GTCGGTGTATGCCTTCTCGG-3′
	R: 5′-AGAGAGACGCGACATTCTCAAT-3′
IL-10	F: 5′-CTTACTGACTGGCATGAGGATCA-3′
	R: 5′-GCAGCTCTAGGAGCATGTGG-3′
IL-18	F: 5′-GACTCTTGCGTCAACTTCAAGG-3′
	R: 5′-CAGGCTGTCTTTTGTCAACGA-3′
Trx	F: 5′-TGCTACGTGGTGTGGACCTTGC-3′
	R: 5′-ACCGGAGAACTCCCCCACCT-3′
IL-6	F: 5′-CTGCAAGAGACTTCCATCCAG-3′
	R: 5′-AGTGGTATAGACAGGTCTGTTGG-3′
TNF-α	F: 5′-CAGGCGGTGCCTATGTCTC-3′
	R: 5′-CGATCACCCCGAAGTTCAGTAG-3′
p38	F: 5′-CTGACCGACGACCACGTTC-3′
	R: 5′-CTTCGTTCACAGCTAGGTTGC-3′
IFN-γ	F: 5′-GGCCTAGCTCTGAGACAATGAAC-3′
	R: 5′-TGACCTCAAACTTGGCAATACTC-3′
Keap1	F: 5′-CGGGGACGCAGTGATGTATG-3′
	R: 5′-TGTGTAGCTGAAGGTTCGGTTA-3′
Nrf2	F: 5′-TAGATGACCATGAGTCGCTTGC-3′
	R: 5′-GCCAAACTTGCTCCATGTCC-3′
HO-1	F: 5′-GATAGAGCGCAACAAGCAGAA-3′
	R: 5′-CAGTGAGGCCCATACCAGAAG-3′
NQO1	F: 5′-AGGATGGGAGGTACTCGAATC-3′
	R: 5′-TGCTAGAGATGACTCGGAAGG-3′
NLRP 3	F: 5′-ATTACCCGCCCGAGAAAGG-3′
	R: 5′-CATGAGTGTGGCTAGATCCAAG-3′
ASC	F: 5′-GACAGTGCAACTGCGAGAAG-3′

	R: 5′-CGACTCCAGATAGTAGCTGACAA-3′
IL-1β	F: 5′-GAAATGCCACCTTTTGACAGTG-3′
	R: 5′-TGGATGCTCTCATCAGGACAG-3′
IκB-α	F: 5′-CGCGGGATGGCCTCAAGAAGGA-3′
	R: 5′-GCCAAGTGCAGGAACGAGTCT-3′
Caspase-1	F: 5′-TGGAAGGTAGGCAAGACT-3′
	R: 5′-ATAGTGGGCATCTGGGTC-3′
NF-κB	F: 5′-ATGGCAGACGATGATCCCTAC-3′
	R: 5′-CGGAATCGAAATCCCCTCTGTT-3′
β-Actin	F: 5′-GAGAAAATCTGGCACCACACCT-3′
	R: 5′- GCACAGCCTGGATAGCAACGTA-3′

Statistical analysis

All data were processed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). One-way ANOVA followed by Duncan's multiple range test was applied to compare differences among groups, with $P < 0.05$ considered statistically significant. Each experiment was performed in triplicate, and results are presented as mean ± standard deviation (SD) [23].

In vitro antioxidant activity of LP-KSFY06

As illustrated in **Figure 2**, LP-KSFY06 displayed significant free radical scavenging activity. For the ABTS assay, scavenging rates ranged from 19.91% to 48.49% for concentrations of 2.5×10^{9} CFU/mL and 2.5×10^{10} CFU/mL. For the DPPH assay, the corresponding scavenging rates were 38.46% to 59.62%. These values were lower than those observed in the positive control group treated with vitamin C (28.39% and 32.26%), yet the scavenging capacity increased clearly with higher LP-KSFY06 concentrations ($p < 0.05$), demonstrating a strong dose-dependent antioxidant effect [23].

odel.

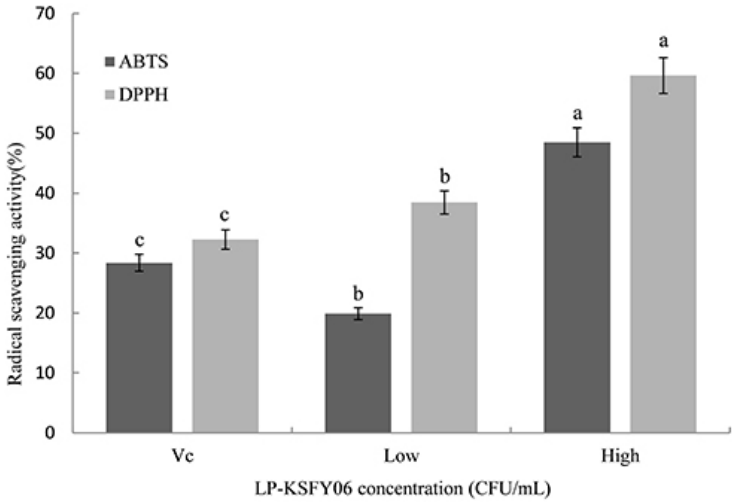

Figure 2. Scavenging activity of LP-KSFY06 against DPPH and ABTS free radicals. LP-KSFY06: Lactobacillus plantarum KSFY06. Low: mice treated with 2.5×10^{9} CFU/mL LP-KSFY06; High: mice treated with 2.5×10^{10} CFU/mL LP-KSFY06. Values with different letters (a–c) within the same column indicate statistically significant differences ($P < 0.05$) as assessed by Duncan's multiple range test [23].

Body weight and organ Index of mice

The organ index serves as an indirect indicator of organ function. No significant differences were observed in body weight among the groups **(Figure 3)**, and all mice survived the experimental period. As shown in **Table 2**, mice in the model group exhibited significant increases in heart, liver, spleen, lung, and kidney indices compared to the normal group due to D-Gal/LPS exposure ($p < 0.05$). Administration of LP-KSFY06 resulted

in a reduction of organ indices in both low- and high-dose groups, with the high-dose group showing a more pronounced decrease ($p < 0.05$). These findings suggest that LP-KSFY06 mitigated organ enlargement and partially alleviated the organ damage induced by D-Gal/LPS [24].

Table 2. Effects of *Lactobacillus plantarum* KSFY06 on Organ Indices in Mice with D-Gal/LPS-Induced Organ Injury (N=10/Group)

Groups	Heart Index	Lung Index	Liver Index	Spleen Index	Kidney Index
Normal	5.85±0.84^{bA}	5.49±1.09^{d}	47.67±2.19^{c}	3.82±1.39^{c}	13.50±1.22^{b}
Model	6.17±1.19^{a}	8.29±1.21^{a}	50.73±2.24^{a}	5.54±1.58^{a}	15.18±2.93^{a}
Low	5.12±0.99^{c}	7.34±1.09^{b}	48.23±2.51^{b}	4.26±1.45^{b}	13.25±1.29^{bc}
High	4.29±0.92^{d}	6.61±0.90^{c}	47.04±2.72^{d}	3.45±1.38^{d}	11.45±1.99^{c}

Notes: Model group: received a single intraperitoneal injection of D-Gal/LPS (250 mg/kg•bw and 25 mg/kg•bw) on the last day. Low-dose group: given daily oral LP-KSFY06 (2.5×10^{9} CFU/kg•bw) for the treatment period, followed by D-Gal/LPS injection on the last day. High-dose group: given daily oral LP-KSFY06 (2.5×10^{10} CFU/kg•bw) before D-Gal/LPS injection on the last day. Values labeled with different letters (a–d) in the same column indicate statistically significant differences ($P < 0.05$) based on Duncan's multiple range test. Data are expressed as mean ± standard deviation (SD). Organ index was calculated as organ weight (mg) divided by body weight (g) [24].

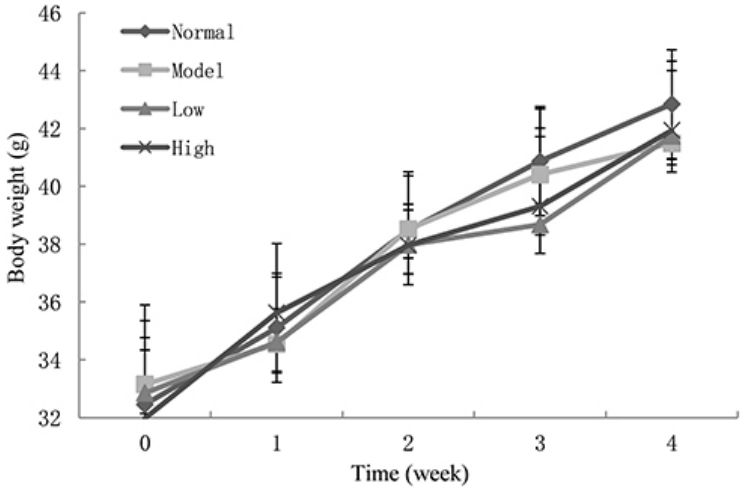

Figure 3. Changes in body weight of mice during the experiment. Low: administered 2.5×10^{9} CFU/mL LP-KSFY06; High: administered 2.5×10^{10} CFU/mL LP-KSFY06.

Histological analysis

The liver is a primary organ for metabolizing toxic substances, and injury induced by D-Gal/LPS causes notable morphological changes [25]. As illustrated in **Figure 4**, liver tissues from the normal group displayed intact architecture, regular hepatocyte arrangement, and a radially structured central vein. In contrast, the model group showed disrupted tissue structure, widespread inflammatory cell infiltration, uneven staining, irregular central veins, cell swelling, loosened cytoplasm, and localized necrosis. Administration of LP-KSFY06 at both low and high doses improved liver histology, with hepatocytes more regularly arranged, only minor morphological alterations, and reduced edema, necrosis, and inflammatory infiltration compared with the model group.

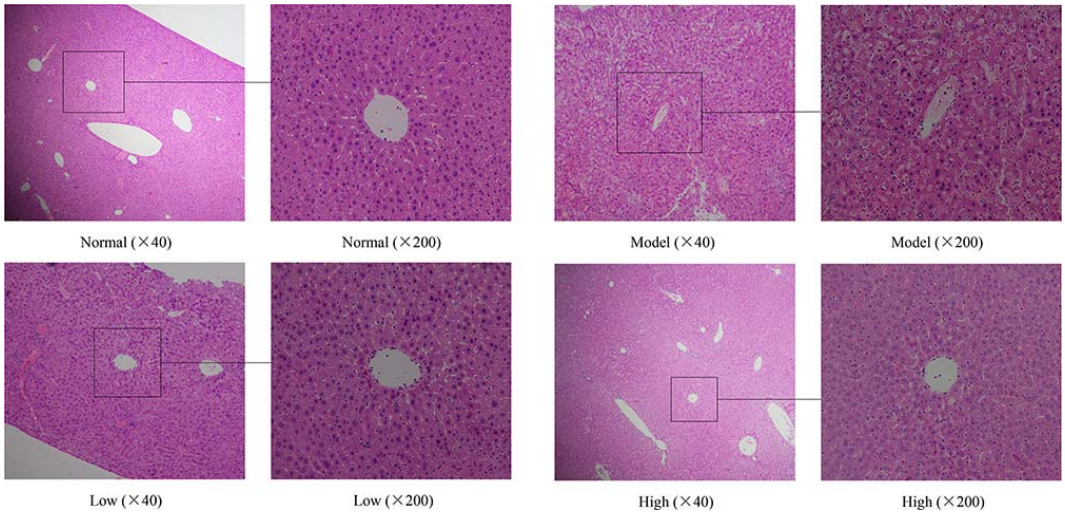

Figure 4. Effects of Lactobacillus plantarum KSFY06 on liver morphology in mice with D-Gal/LPS-induced injury. Model: D-Gal/LPS-induced group (250 mg/kg•bw, 25 mg/kg•bw); Low: LP-KSFY06 (2.5×10^9 CFU/kg•bw); High: LP-KSFY06 (2.5×10^{10} CFU/kg•bw).

In the normal control group, spleen tissue showed intact cells, well-defined architecture, clear medulla-cortex boundaries, orderly cell arrangement, and no evidence of degeneration or necrosis **(Figure 5)** [25]. By contrast, the model group exhibited pronounced spleen damage, including distorted morphology, disorganized tissue structure, expansion of the splenic cord and red pulp sinus, congestion, increased red blood cell content, reduced lymphocytes in white pulp, nuclear fragmentation in white pulp, and compressed red cords with a loose arrangement. In the LP-KSFY06-treated groups, these pathological changes were markedly improved. Spleen congestion was alleviated, white pulp was dispersed throughout the splenic parenchyma, and the boundaries between white and red pulp were distinct. These histological findings of both liver and spleen suggest that LP-KSFY06 may help prevent tissue damage associated with oxidative stress and aging.

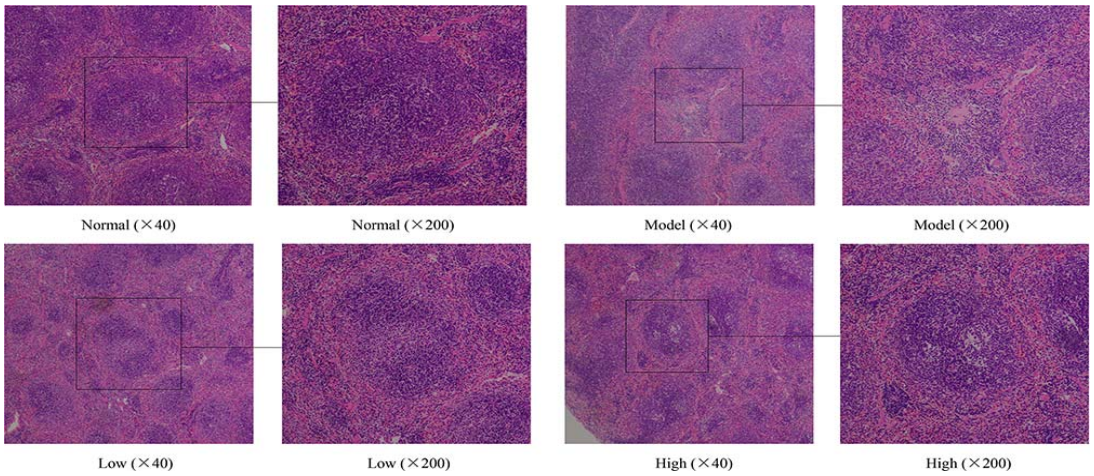

Figure 5. Effects of Lactobacillus plantarum KSFY06 on spleen morphology in mice with D-Gal/LPS-induced injury. Model: D-Gal/LPS-treated group (250 mg/kg•bw, 25 mg/kg•bw); Low: LP-KSFY06 (2.5×10^9 CFU/kg•bw); High: LP-KSFY06 (2.5×10^{10} CFU/kg•bw).

Serum and liver tissue liver function indicators

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serve as sensitive biomarkers for hepatic injury [26]. In this study, AST and ALT concentrations in both serum and liver tissue were markedly elevated in the D-Gal/LPS-treated model group ($P < 0.05$). Oral administration of LP-KSFY06 effectively restored these enzyme levels toward normal, indicating its protective effect against liver injury.

Table 3. Levels of AST and ALT in Serum and Liver Tissue of Mice (N=10/Group)

Groups	AST		ALT	
	Serum (U/L)	Liver (U/g prot)	Serum (U/L)	Liver (U/g prot)
Normal	8.66 ± 1.05^{dA}	20.97 ± 1.02^{c}	11.09 ± 1.21^{c}	53.85 ± 1.87^{c}
Model	15.12 ± 1.34^{a}	26.95 ± 1.88^{a}	18.46 ± 1.94^{a}	73.24 ± 1.94^{a}
Low	13.31 ± 1.16^{b}	22.56 ± 1.64^{b}	14.79 ± 1.59^{b}	58.55 ± 1.65^{b}
High	9.69 ± 1.29^{c}	19.93 ± 1.95^{cd}	11.03 ± 1.24^{c}	41.18 ± 1.57^{d}

Notes: Model: treated with D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw, last day) injection; Low: mice treated with D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw, last day) injection after *Lactobacillus plantarum* KSFY06 (2.5×10^{9} CFU/kg·bw, per day) oral administration; High: treated with D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw, last day) injection after *Lactobacillus plantarum* KSFY06 (2.5×10^{10} CFU/kg·bw, per day) oral administration. $^{a-d}$There was significant difference in different letters in the same column ($P < 0.05$), which was determined by Duncan's multiple range test. ^{A}Values presented are the mean±standard deviation (SD).

Levels of SOD, CAT, GSH-Px, GSH, T-AOC, NO, MDA, and MPO in mouse serum and liver

As presented in **Figures 6 and 7**, mice in the model group exhibited a significant reduction in antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), total antioxidant capacity (T-AOC), and glutathione (GSH), compared with the normal group. Conversely, oxidative stress markers, such as malondialdehyde (MDA), nitric oxide (NO), and myeloperoxidase (MPO), were markedly elevated in the model group ($P < 0.05$). Administration of Lactobacillus plantarum KSFY06 mitigated the decrease in antioxidant enzymes and GSH content while reducing MDA, NO, and MPO levels, with the higher dose showing a more pronounced effect. These results indicate that supplementation with LP-KSFY06 as an exogenous antioxidant can enhance endogenous antioxidant levels and activities, effectively suppressing oxidative damage and potentially preventing age-related diseases associated with oxidative stress [27].

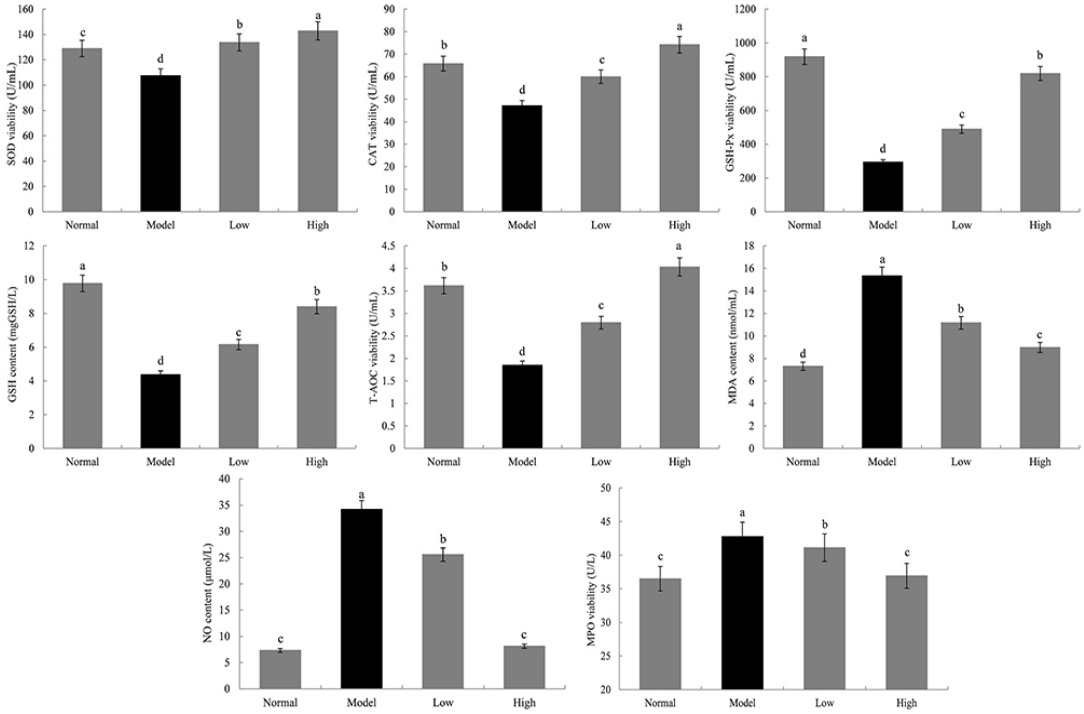

Figure 6. Effects of *Lactobacillus plantarum* KSFY06 on SOD, CAT, GSH-Px, GSH, T-AOC, MPO, MDA, and NO in serum of mice injured by D-Gal/LPS. $^{a-d}$There was significant difference in different letters in the same column ($P < 0.05$), which was determined by Duncan's multiple range test. Model: group induced by D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw); Low: treated with LP-KSFY06 (2.5×10^{9} CFU/kg·bw); High: treated with LP-KSFY06 (2.5×10^{10} CFU/kg·bw).

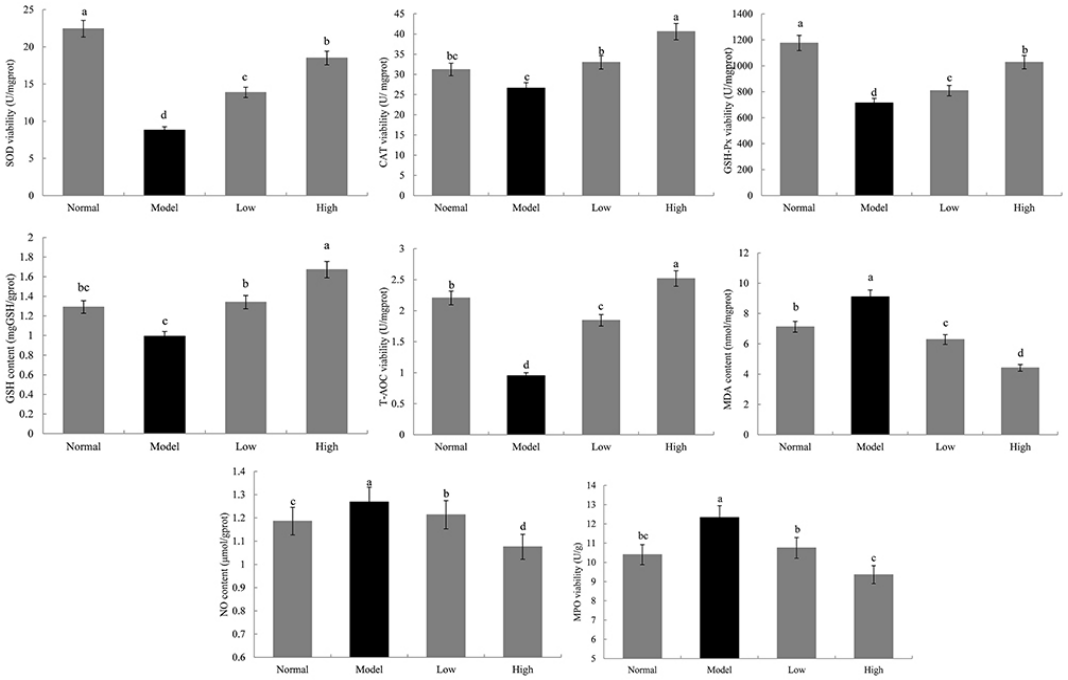

Figure 7. Effects of *Lactobacillus plantarum* KSFY06 on SOD, CAT, GSH-Px, GSH, T-AOC, MPO, MDA, and NO in liver of mice injured by D-Gal/LPS. [a–d]There was significant difference in different letters in the same column ($P < 0.05$), which was determined by Duncan's multiple range test. Model: group induced by D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw); Low: treated with LP-KSFY06 (2.5×10^9 CFU/kg·bw); High: treated with LP-KSFY06 (2.5×10^{10} CFU/kg·bw).

Cytokine levels in mouse serum and liver

As shown in **Table 4**, pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and interferon-γ (IFN-γ), were significantly elevated in the serum and liver of the model group compared with the normal group ($P < 0.05$), while the anti-inflammatory cytokine interleukin-10 (IL-10) was reduced. Administration of Lactobacillus plantarum KSFY06 effectively reversed these changes, decreasing the levels of pro-inflammatory cytokines and increasing IL-10, indicating that LP-KSFY06 can alleviate the inflammatory response induced by D-Gal/LPS in mice [27].

Table 4. Levels of IL-6, IL-10, IL-1β, TNF-α and IFN-γ in Serum and Liver Tissue of Mice (N=10/Group)

	IL-6		**IL-10**		**IL-1β**		**TNF-α**		**IFN-γ**	
roups	**Serum (pg/mL)**	**Liver (pg/mgprot)**	**Serum (pg/mL)**	**Liver (pg/mgprot)**	**Serum (pg/mL)**	**Liver (pg/mgprot)**	**Serum (pg/mL)**	**Liver (pg/mL)**	**Serum (pg/mL)**	**Liver (pg/mL)**
Normal	5.68 ± 0.71^{bA}	4.98 ± 0.47^{b}	58.00 ± 3.83^{c}	176.85 ± 17.49^{a}	21.19 ± 3.35^{b}	12.92 ± 1.34^{c}	61.57 ± 7.32^{c}	84.29 ± 17.37^{d}	86.17 ± 6.76^{c}	80.48 ± 8.37^{d}
Model	8.69 ± 1.34^{a}	6.39 ± 0.54^{a}	45.11 ± 4.76^{d}	124.19 ± 11.96^{d}	26.21 ± 5.08^{a}	16.20 ± 1.62^{a}	97.85 ± 10.38^{a}	119.32 ± 19.4^{a}	110.70 ± 15.41^{a}	112.76 ± 12.34^{a}

Low	5.71±0.49^{b}	4.81±0.37^{bc}	60.68±4.38^{b}	137.81±15.94^{c}	19.30±1.84^{c}	15.02±1.05^{b}	82.98±5.71^{b}	107.11±18.13^{b}	90.64±7.37^{b}	100.25±16.22^{b}
High	4.16±1.29^{c}	4.42±0.65^{c}	78.06±7.22^{a}	146.85±19.84^{b}	13.94±2.07^{d}	12.45±2.47^{cd}	54.49±6.95^{c}	97.87±11.18^{c}	65.38±6.38^{c}	85.31±13.85^{c}

Notes: Model: treated with D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw, last day) injection; Low: mice treated with D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw, last day) injection after *Lactobacillus plantarum* KSFY06 (2.5×10^{9} CFU/kg·bw, per day) oral administration; High: treated with D-Gal/LPS (250 mg/kg·bw and 25 mg/kg·bw, last day) injection after *Lactobacillus plantarum* KSFY06 (2.5×10^{10} CFU/kg·bw, per day) oral administration. $^{a-d}$There was significant difference in different letters in the same column ($P < 0.05$), which was determined by Duncan's multiple range test. ^{A}Values presented are the mean±standard deviation (SD).

Effects of lactobacillus plantarum KSFY06 on hepatic gene expression related to oxidation, inflammation, and apoptosis (RT-qPCR analysis)

As shown in **Figure 8**, in the D-Gal/LPS-induced acute liver injury model, the mRNA levels of antioxidant-related genes—including Cu/Zn-superoxide dismutase (SOD1), Mn-superoxide dismutase (SOD2), glutathione (GSH), glutathione peroxidase (GSH-Px), catalase (CAT), thioredoxin (Trx), and the anti-inflammatory cytokine IL-10—were significantly reduced compared with the normal group, whereas pro-inflammatory cytokines such as IFN-γ, IL-6, IL-18, IL-1β, TNF-α, and Mapk14 were markedly elevated ($P < 0.05$). Treatment with LP-KSFY06 effectively restored the expression of these genes, demonstrating a protective role against D-Gal/LPS-induced liver injury [28].

Additionally, the model group exhibited increased expression of NLRP3, ASC, caspase-1, and NF-κB mRNA, with a concurrent decrease in IκB-α mRNA, compared to normal controls. LP-KSFY06 administration significantly reduced the expression of NLRP3, ASC, caspase-1, and NF-κB while upregulating IκB-α ($P < 0.05$), suggesting that its protective effects may involve modulation of the NLRP3/NF-κB signaling pathway [29].

Regarding oxidative stress pathways, Keap1 expression was elevated and Nrf2, HO-1, and NQO1 expression was suppressed in the model group relative to the normal group. LP-KSFY06 treatment decreased Keap1 expression, which led to the activation of Nrf2, enhanced transcription of downstream antioxidant genes HO-1 and NQO1, and alleviated oxidative damage ($P < 0.05$). These results indicate that LP-KSFY06 mitigates oxidative stress through regulation of the Keap1-Nrf2/ARE pathway [30].

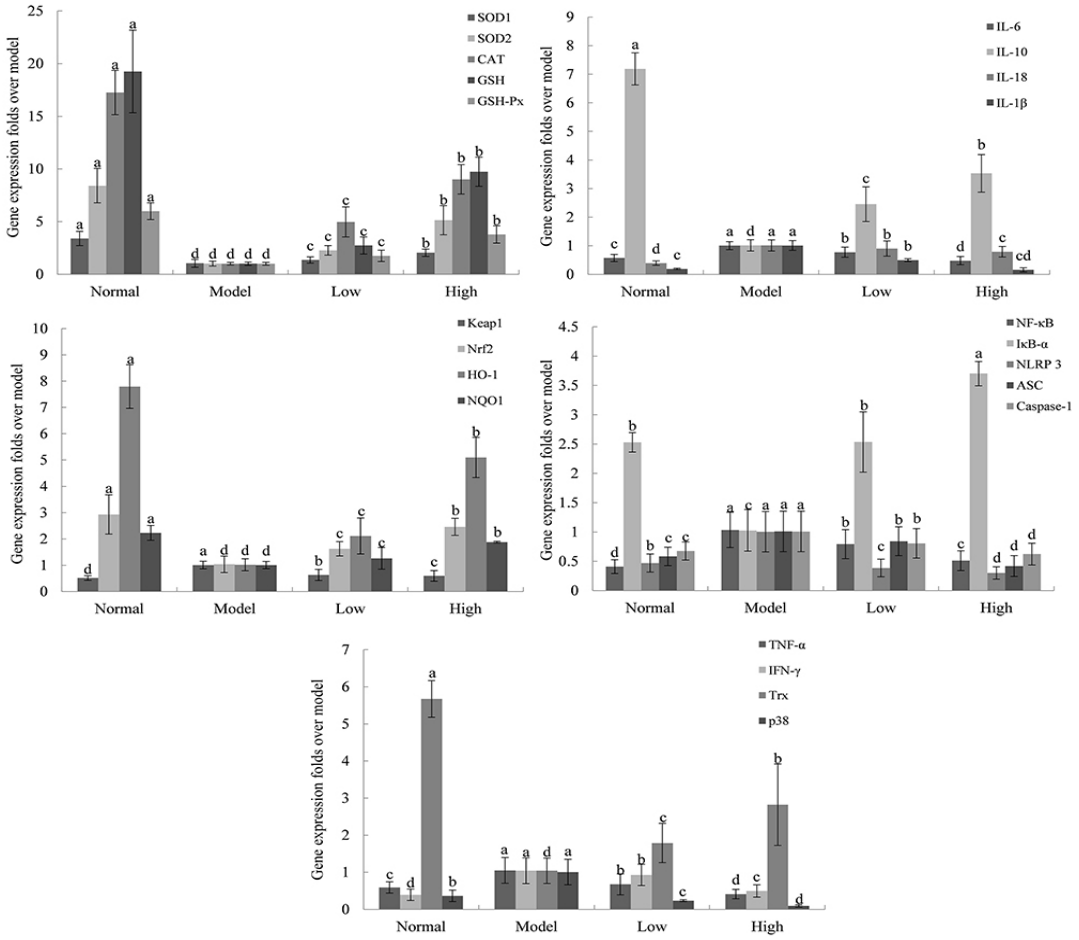

Figure 8. Effects of *Lactobacillus plantarum* KSFY06 on the mRNA expression in liver tissue of mice. [a–d]There was significant difference in different letters in the same column ($P < 0.05$), which was determined by Duncan's multiple range test. Model: group induced by D-Gal/LPS (250 mg/kg·bw, 25 mg/kg·bw); Low: low-dose group, 2.5×10^9 CFU/kg·bw; High: high-dose group, 2.5×10^{10} CFU/kg·bw.

Results and Discussion

Lactobacillus is a widely distributed probiotic with diverse species, and certain strains exhibit important biological activities, including antioxidant effects, endotoxin neutralization, anti-aging, anti-cancer properties, and immune regulation [28–32]. In this study, Lactobacillus plantarum KSFY06 (LP-KSFY06) was isolated from naturally fermented cattle milk produced by the Kashi Herdsman Family in Xinjiang. This yogurt is derived from a unique ecological environment characterized by large temperature fluctuations and strong ultraviolet radiation, which may contribute to the distinct properties of the isolated strain compared with typical Lactobacillus strains [33]. Prior experiments demonstrated that LP-KSFY06 maintains viability in simulated gastric juice and bile salt conditions.

Acute liver injury (ALI) is a common liver syndrome caused by viruses, alcohol, drugs, and other factors, leading to hepatocyte swelling, inflammation, and necrosis [34]. D-Gal/LPS-induced liver injury models are widely used to evaluate antioxidants, anti-aging agents, plant extracts, and probiotics, as this model primarily involves oxidative stress and inflammatory responses [35–38]. Prolonged galactose administration disrupts metabolism, alters cellular osmotic balance, causes hepatocyte swelling, and induces oxidative stress, resulting in liver damage [39]. LPS, an endotoxin, is mainly cleared by Kupffer cells, which, when activated, produce reactive oxygen species (ROS) such as hydrogen peroxide and release inflammatory mediators like ILs and TNF-α, thereby inducing hepatocyte necrosis [40]. In this study, D-Gal/LPS treatment led to significant hepatocyte necrosis, inflammatory infiltration (lymphocytes and macrophages), and structural disorganization around the central vein.

LP-KSFY06 administration markedly alleviated these pathological changes, demonstrating a protective effect on liver injury.

Organ weights and organ indexes reflect the extent of tissue damage. LP-KSFY06 mitigated the D-Gal/LPS-induced increase in organ indexes [41]. ALT is highly sensitive in the early stage of ALI and indicates hepatocyte parenchymal injury, while AST reflects the severity of liver damage [42]. LP-KSFY06 prevented the elevation of serum and hepatic ALT and AST levels.

Antioxidant enzymes play critical roles in cellular redox balance. SOD catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide through electron transfer between metal ions, maintaining oxidative homeostasis [43]. CAT decomposes H2O2 into H2O and O2, protecting cells from oxidative damage and working synergistically with SOD [44]. GSH is a major non-enzymatic antioxidant that regulates intracellular redox balance [45]. GSH-Px catalyzes the conversion of GSH to GSSG, collectively helping to prevent oxidative edema and delay oxidative aging [46]. In this study, LP-KSFY06 enhanced the activity of SOD, CAT, GSH-Px, and GSH, supporting antioxidant defense.

Oxidative stress generates free radicals that initiate lipid peroxidation, producing MDA as a final product. MDA can cross-link proteins, nucleic acids, and other macromolecules, causing cytotoxicity and impairing normal biochemical processes [47]. NO is a lipophilic molecule that rapidly diffuses through membranes and plays key roles in cardiovascular and cerebral regulation [48]. MPO, derived from polymorphonuclear neutrophils, monocytes, and macrophages, is released upon leukocyte activation and degranulation, contributing to immune defense and tissue injury in conditions such as leukemia, vasculitis, and Alzheimer's disease [49]. D-Gal/LPS-induced oxidative stress disrupted normal metabolism, increasing MDA, NO, and MPO levels, which LP-KSFY06 effectively reduced, highlighting its antioxidant activity.

As liver injury worsens, oxidative stress increases, impairing immune function and promoting the release of inflammatory cytokines. Oxidative stress can activate hepatic stellate cells (HSCs) and Kupffer cells, creating a positive feedback loop that amplifies cytokine production and exacerbates liver damage [50]. Key immunoregulatory cytokines include IL-1β, IL-6, IL-10, TNF-α, and IFN-γ, whose secretion is associated with Th1/Th2 cell responses. IFN-γ is mainly secreted by Th1 cells, while IL-6 and IL-10 are secreted by Th2 cells [51]. TNF-α and IL-6 act on hepatocyte surface receptors and induce hepatocyte necrosis, with TNF-α being a primary mediator of inflammation and IL-6 promoting acute-phase protein and T-cell accumulation [52, 53]. IL-1β, produced by innate immune cells, is processed intracellularly via caspase-1 [54]. IFN-γ inhibits Th2 differentiation, while IL-10 suppresses Th1 responses; under inflammation, this regulatory balance is disrupted [55]. In this study, LP-KSFY06 reduced TNF-α, IFN-γ, IL-6, and IL-1β while increasing IL-10 levels, thereby attenuating inflammatory stress in liver-injured mice.

The Keap1-Nrf2/ARE pathway is recognized as a key endogenous antioxidant signaling route. Under normal conditions, Nrf2 binds primarily to its inhibitor Keap1 and remains inactive in the cytoplasm, where it is quickly degraded via the ubiquitin-proteasome system, maintaining low basal transcriptional activity of Nrf2. D-Gal/LPS treatment upregulated the negative regulator Keap1 while suppressing the expression of Nrf2, HO-1, and NQO1. Administration of LP-KSFY06 activated the Nrf2/ARE pathway, decreased Keap1 levels, facilitated the release of nuclear Nrf2, enhanced the binding of Nrf2 to ARE, and subsequently stimulated the expression of downstream antioxidant enzymes and phase II detoxification genes, thereby improving the body's antioxidant defense. Nrf2 serves as a critical transcription factor regulating cellular oxidative stress responses, mitigating ROS- and electrophile-induced damage, maintaining cellular stability, and promoting redox homeostasis through induction of antioxidant proteins. HO-1, a stress-inducible protein, is involved in heme metabolism, inflammation, and antioxidant processes, and also offers protective effects on cardiovascular and nervous system function [56–58].

NF-κB, a member of the Rel protein family, mainly exists as a p65/p50 heterodimer. In its inactive state, it forms a trimer with IκB-α. D-Gal/LPS triggers a cascade of protein kinase activations, including IκB kinase complex activation, resulting in IκB-α ubiquitination and degradation, which subsequently promotes NLRP3 inflammasome formation and induces inflammatory responses. NLRP3 inflammasomes activate caspase-1, which then processes pro-inflammatory cytokines such as IL-1β, initiating the host inflammatory reaction [59–61]. Previous studies have confirmed the critical role of the NF-κB/NLRP3 pathway in ALI-related inflammation [62]. In this study, LP-KSFY06 treatment increased IκB-α expression and suppressed NF-κB, NLRP3, ASC, and caspase-1 expression, indicating inhibition of this inflammatory pathway.

Overall, the anti-oxidant and anti-inflammatory properties of LP-KSFY06 were demonstrated at the molecular, histological, and gene expression levels. Protein-level mechanisms were not assessed in this study but are planned for future investigations.

Conclusion

LP-KSFY06 effectively mitigated D-Gal/LPS-induced ALI, enhanced antioxidant enzyme activities in serum and liver, reduced peroxide accumulation, and elevated immunoregulatory cytokine levels. Its protective mechanism involves boosting endogenous antioxidant defenses and modulating immune responses. Specifically, LP-KSFY06 activates the Nrf2/ARE pathway while suppressing the NF-κB/NLRP3 signaling cascade, contributing to its hepatoprotective effects.

Acknowledgments: This research was funded by Chongqing University Innovation Research Group Project (CXQTP20033), the Science and Technology Project of Chongqing Education Commission (KJQN202001604) and the Research Project of Chongqing University of Education (KY201920C), China.

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut. 2017;66(3):541-53. doi:10.1136/gutjnl-2016-312670
2. Tian Z, Chen Y, Yao N, Hu C, Wu Y, Guo D. Role of mitophagy regulation by ROS in hepatic stellate cells during acute liver failure. Am J Physiol Gastrointest Liver Physiol. 2018;315(3):G374-84. doi:10.1152/ajpgi.00032.2018
3. Dechêne A, Sowa JP, Gieseler RK, Jochum C, Bechmann LP, El Fouly A, et al. Acute liver failure is associated with elevated liver stiffness and hepatic stellate cell activation. Hepatology. 2010;52(3):1008-16. doi:10.1002/hep.23754
4. Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, and diseases. Clin Interv Aging. 2018;13:757-72. doi:10.2147/CIA.S158513
5. Mattout A, Dechat T, Adam SA, Goldman RD, Gruenbaum Y. Nuclear lamins, diseases and aging. Curr Opin Cell Biol. 2006;18(3):335-41. doi:10.1016/j.ceb.2006.03.007
6. Crunkhorn S. Neurodegenerative disorders: restoring the balance. Nat Rev Drug Discov. 2011;10(8):576. doi:10.1038/nrd3521
7. Sas K, Robotka H, Toldi J, Vécsei L. Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders. J Neurol Sci. 2007;257(1-2):221-39. doi:10.1016/j.jns.2007.01.033
8. Kurien BT, Hensley K, Bachmann M, Scofield RH. Oxidatively modified autoantigens in autoimmune diseases. Free Radic Biol Med. 2006;41(4):549-56. doi:10.1016/j.freeradbiomed.2006.05.020
9. Okada K, Warabi E, Sugimoto H, Horie M, Tokushige K, Ueda T, et al. Nrf2 inhibits hepatic iron accumulation and counteracts oxidative stress-induced liver injury in nutritional steatohepatitis. J Gastroenterol. 2012;47(8):924-35. doi:10.1007/s00535-012-0552-9
10. Suzuki M, Otsuki A, Keleku-Lukwete N, Yamamoto M. Overview of redox regulation by Keap1-Nrf2 system in toxicology and cancer. Curr Opin Toxicol. 2016;1:29-36. doi:10.1016/j.cotox.2016.10.001
11. Dong F, Wang S, Wang Y, Yang X, Jiang J, Gao D, et al. Quercetin ameliorates learning and memory via the Nrf2-ARE signaling pathway in D-galactose-induced neurotoxicity in mice. Biochem Biophys Res Commun. 2017;491(3):636-41. doi:10.1016/j.bbrc.2017.07.151

12. Liang N, Sang Y, Liu W, Yu W, Wang X. Anti-inflammatory effects of gingerol on lipopolysaccharide-stimulated RAW 264.7 cells by inhibiting NF-κB signaling pathway. Inflammation. 2018;41(3):835-45. doi:10.1007/s10753-018-0737-3
13. Wang CC, Cheng PY, Peng YJ, Wu ES, Wei HP, Yen MH. Naltrexone protects against lipopolysaccharide/D-galactosamine-induced hepatitis in mice. J Pharmacol Sci. 2008;108(3):239-47. doi:10.1254/jphs.08096FP
14. Choi JW, Kim IH, Kim YM, Lee MK, Nam TJ. Pyropia yezoensis glycoprotein regulates antioxidant status and prevents hepatotoxicity in a rat model of D-galactosamine/lipopolysaccharide-induced acute liver failure. Mol Med Rep. 2016;13(4):3110-4. doi:10.3892/mmr.2016.4932
15. Shakil A, Kramer D, Mazariegos G, Fung J, Rakela J. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. Liver Transpl. 2000;6(2):163-9. doi:10.1016/S1527-6465(00)80005-2
16. Comert ED, Gokmen V. Evolution of food antioxidants as a core topic of food science for a century. Food Res Int. 2018;105:76-93. doi:10.1016/j.foodres.2017.10.056
17. Ge Q, Ge P, Jiang D, Du N, Chen J, Zhang Y, et al. A novel and simple cell-based electrochemical biosensor for evaluating the antioxidant capacity of Lactobacillus plantarum strains isolated from Chinese dry-cured ham. Biosens Bioelectron. 2018;99:555-63. doi:10.1016/j.bios.2017.08.037
18. Marazza JA, Nazareno MA, de Giori GS, Garro MS. Enhancement of the antioxidant capacity of soymilk by fermentation with Lactobacillus rhamnosus. J Funct Foods. 2012;4(3):594-601. doi:10.1016/j.jff.2012.03.005
19. Persichetti E, De Michele A, Codini M, Traina G. Antioxidative capacity of Lactobacillus fermentum LF31 evaluated in vitro by oxygen radical absorbance capacity assay. Nutrition. 2014;30(7-8):936-8. doi:10.1016/j.nut.2013.12.009
20. Fardet A, Rock E. In vitro and in vivo antioxidant potential of milks, yoghurts, fermented milks and cheeses: a narrative review of evidence. Nutr Res Rev. 2018;31(1):52-70. doi:10.1017/S0954422417000191
21. Zhao X, Wang Q, Li G, Chen F, Qian Y, Wang R. In vitro antioxidant, anti-mutagenic, anti-cancer and anti-angiogenic effects of Chinese Bowl tea. J Funct Foods. 2014;7:590-8. doi:10.1016/j.jff.2013.12.026
22. Zhang H, Yang YF, Zhou ZQ. Phenolic and flavonoid contents of mandarin (Citrus reticulata Blanco) fruit tissues and their antioxidant capacity as evaluated by DPPH and ABTS methods. J Integr Agric. 2018;17(1):256-63. doi:10.1016/S2095-3119(17)61664-2
23. Suo H, Sun P, Wang C, Peng D, Zhao X. Apoptotic effects of insect tea in HepG2 human hepatoma cells. CyTA J Food. 2016;14(2):169-75. doi:10.1080/19476337.2015.1076521
24. Khan SS, Singer BD, Vaughan DE. Molecular and physiological manifestations and measurement of aging in humans. Aging Cell. 2017;16(4):624-33. doi:10.1111/acel.12601
25. Li W, Shi J, Papa F, Maggi F, Chen X. Isofuranodiene, the main volatile constituent of wild celery (Smyrnium olusatrum L.), protects D-galactosamine/lipopolysaccharide-induced liver injury in rats. Nat Prod Res. 2016;30(10):1162-5. doi:10.1080/14786419.2015.1041139
26. Shidfar F, Bahrololumi SS, Doaei S, Mohammadzadeh A, Gholamalizadeh M, Mohammadimanesh A. The effects of extra virgin olive oil on alanine aminotransferase, aspartate aminotransferase, and ultrasonographic indices of hepatic steatosis in nonalcoholic fatty liver disease patients undergoing low calorie diet. Can J Gastroenterol Hepatol. 2018;2018:1053710. doi:10.1155/2018/1053710
27. Mittler R. Oxidative stress, antioxidants and stress tolerance. Trends Plant Sci. 2002;7(9):405-10. doi:10.1016/S1360-1385(02)02312-9
28. Chiva M, Soriano G, Rochat I, Peralta C, Rochat F, Llovet T, et al. Effect of Lactobacillus johnsonii La1 and antioxidants on intestinal flora and bacterial translocation in rats with experimental cirrhosis. J Hepatol. 2002;37(4):456-62. doi:10.1016/S0168-8278(02)00142-3
29. Korhonen R, Kosonen O, Korpela R, Moilanen E. The expression of COX2 protein induced by Lactobacillus rhamnosus GG, endotoxin and lipoteichoic acid in T84 epithelial cells. Lett Appl Microbiol. 2004;39(1):19-24. doi:10.1111/j.1472-765X.2004.01531.x
30. Lin X, Xia Y, Wang G, Xiong Z, Zhang H, Lai F, et al. Lactobacillus plantarum AR501 alleviates the oxidative stress of D-galactose-induced aging mice liver by upregulation of Nrf2-mediated antioxidant enzyme expression. J Food Sci. 2018;83(7):1990-8. doi:10.1111/1750-3841.14200

31. Otani TT, Briley MR, Geran RI. Use of a Lactobacillus casei assay as a prescreen for potential anticancer agents: an update study. J Pharm Sci. 1984;73(2):264-5. doi:10.1002/jps.2600730232
32. Gill HS, Rutherfurd KJ, Prasad J, Gopal PK. Enhancement of natural and acquired immunity by Lactobacillus rhamnosus (HN001), Lactobacillus acidophilus (HN017) and Bifidobacterium lactis (HN019). Br J Nutr. 2000;83(2):167-76. doi:10.1017/S0007114500000210
33. Wang Y, Zhou J, Xia X, Zhao Y, Shao W. Probiotic potential of Lactobacillus paracasei FM-LP-4 isolated from Xinjiang camel milk yoghurt. Int Dairy J. 2016;62:28-34. doi:10.1016/j.idairyj.2016.07.001
34. Khan R, Koppe S. Modern management of acute liver failure. Gastroenterol Clin North Am. 2018;47(2):313-26. doi:10.1016/j.gtc.2018.01.005
35. Li F, Miao L, Sun H, Zhang Y, Bao X, Zhang D. Establishment of a new acute-on-chronic liver failure model. Acta Pharm Sin B. 2017;7(3):326-33. doi:10.1016/j.apsb.2016.09.003
36. Liu H, Zhang W, Dong S, Song Z, Bai Y, Li X, et al. Protective effects of sea buckthorn polysaccharide extracts against LPS/D-GalN-induced acute liver failure in mice via suppressing TLR4-NF-κB signaling. J Ethnopharmacol. 2015;176:69-78. doi:10.1016/j.jep.2015.10.029
37. Wang SF, Fang HY, Qu HB. Optimization of micellar electrokinetic capillary chromatography method using central composite design for the analysis of components in Yangwei granule. J Zhejiang Univ Sci B. 2011;12(3):193-200. doi:10.1631/jzus.B1000135
38. Truusalu K, Kullisaar T, Hütt P, Mikelsaar M, Zilmer K, Rehema A, et al. Immunological, antioxidative, and morphological response in combined treatment of ofloxacin and Lactobacillus fermentum ME-3 probiotic in Salmonella Typhimurium murine model. APMIS. 2010;118(11):864-72. doi:10.1111/j.1600-0463.2010.02672.x
39. Zhang ZF, Fan SH, Zheng YL, Lu J, Wu DM, Shan Q, et al. Purple sweet potato color attenuates oxidative stress and inflammatory response induced by D-galactose in mouse liver. Food Chem Toxicol. 2009;47(2):496-501. doi:10.1016/j.fct.2008.12.005
40. Ohshima T, Mukai R, Nakahara N, Ishizu K, Yamamoto H, Miyoshi N, et al. HTLV-1 basic leucine-zipper factor, HBZ, interacts with MafB and suppresses transcription through a Maf recognition element. J Cell Biochem. 2010;111(1):187-94. doi:10.1002/jcb.22687
41. Tang T, He B. Treatment of D-galactose induced mouse aging with Lycium barbarum polysaccharides and its mechanism study. Afr J Tradit Complement Altern Med. 2013;10(4):12-7. doi:10.4314/ajtcam.v10i4.3
42. Josekutty J, Iqbal J, Iwawaki T, Kohno K, Hussain MM. Microsomal triglyceride transfer protein inhibition induces endoplasmic reticulum stress and increases gene transcription via Ire1α/cJun to enhance plasma ALT/AST. J Biol Chem. 2013;288(20):14372-83. doi:10.1074/jbc.M113.459602
43. McCord JM, Edeas MA. SOD, oxidative stress and human pathologies: a brief history and a future vision. Biomed Pharmacother. 2005;59(4):139-42. doi:10.1016/j.biopha.2005.03.005
44. Sepasi Tehrani H, Moosavi-Movahedi AA. Catalase and its mysteries. Prog Biophys Mol Biol. 2018;140:5-12. doi:10.1016/j.pbiomolbio.2018.03.001
45. Wilke BC, Vidailhet M, Favier A, Guillemin F, Duc M, Arnaud J, et al. Selenium, glutathione peroxidase (GSH-Px) and lipid peroxidation products before and after selenium supplementation. Clin Chim Acta. 1992;207(1-2):137-42. doi:10.1016/0009-8981(92)90157-L
46. Li JE, Nie SP, Xie MY, Huang DF, Wang YT, Li C. Chemical composition and antioxidant activities in immunosuppressed mice of polysaccharides isolated from Mosla chinensis Maxim cv. Jiangxiangru. Int Immunopharmacol. 2013;17(2):267-74. doi:10.1016/j.intimp.2013.05.033
47. Draper HH, Hadley M. Malondialdehyde determination as index of lipid peroxidation. Methods Enzymol. 1990;186:421-31. doi:10.1016/0076-6879(90)86135-I
48. Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiol Rev. 2007;87(1):315-424. doi:10.1152/physrev.00029.2006
49. Kizaki M, Miller CW, Selsted ME, Koeffler HP. Myeloperoxidase (MPO) gene mutation in hereditary MPO deficiency. Blood. 1994;83(7):1935-40.
50. Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. J Clin Invest. 2005;115(10):2656-64. doi:10.1172/JCI26373

51. Liu Y, Jiao F, Qiu Y, Li W, Lao F, Zhou G, et al. The effect of Gd@C82(OH)22 nanoparticles on the release of Th1/Th2 cytokines and induction of TNF-α mediated cellular immunity. Biomaterials. 2009;30(23-24):3934-45. doi:10.1016/j.biomaterials.2009.03.064
52. Chen J, Liu GZ, Sun Q, Ding X, Zhang Y, Li Y. Protective effects of ginsenoside Rg3 on TNF-α-induced human nucleus pulposus cells through inhibiting NF-κB signaling pathway. Life Sci. 2019;216:1-9. doi:10.1016/j.lfs.2018.11.022
53. Taher MY, Davies DM, Maher J. The role of the interleukin (IL)-6/IL-6 receptor axis in cancer. Biochem Soc Trans. 2018;46(6):1449-62. doi:10.1042/BST20180136
54. Swaroop S, Mahadevan A, Shankar SK, Adlakha YK, Basu A. Correction to: HSP60 critically regulates endogenous IL-1β production in activated microglia by stimulating NLRP3 inflammasome pathway. J Neuroinflammation. 2018;15(1):317. doi:10.1186/s12974-018-1355-6
55. Brodacki B, Staszewski J, Toczyłowska B, Kozłowska E, Drela N, Chalimoniuk M, et al. Serum interleukin (IL-2, IL-10, IL-6, IL-4), TNFα, and INFγ concentrations are elevated in patients with atypical and idiopathic parkinsonism. Neurosci Lett. 2008;441(2):158-62. doi:10.1016/j.neulet.2008.06.040
56. De Freitas Silva M, Pruccoli L, Morroni F, Sita G, Seghetti F, Viegas C, et al. The Keap1/Nrf2-ARE pathway as a pharmacological target for chalcones. Molecules. 2018;23(7):1803. doi:10.3390/molecules23071803
57. Bellezza I, Giambanco I, Minelli A, Donato R. Nrf2-Keap1 signaling in oxidative and reductive stress. Biochim Biophys Acta Mol Cell Res. 2018;1865(5):721-33. doi:10.1016/j.bbamcr.2018.02.010
58. Zhang J, Fu B, Zhang X, Zhang L, Bai X, Zhao X, et al. Bicyclol upregulates transcription factor Nrf2, HO-1 expression and protects rat brains against focal ischemia. Brain Res Bull. 2014;100:38-43. doi:10.1016/j.brainresbull.2013.11.001
59. Liu RT, Wang A, To E, Gao J, Cao S, Cui JZ, et al. Vinpocetine inhibits amyloid-beta induced activation of NF-κB, NLRP3 inflammasome and cytokine production in retinal pigment epithelial cells. Exp Eye Res. 2014;127:49-58. doi:10.1016/j.exer.2014.07.003
60. Sun Y, Zhao Y, Yao J, Zhao L, Wu Z, Wang Y, et al. Wogonoside protects against dextran sulfate sodium-induced experimental colitis in mice by inhibiting NF-κB and NLRP3 inflammasome activation. Biochem Pharmacol. 2015;94(2):142-54. doi:10.1016/j.bcp.2015.02.002
61. Long L, Pang XX, Lei F, Zhang JS, Wang W, Liao LD, et al. SLC52A3 expression is activated by NF-κB p65/Rel-B and serves as a prognostic biomarker in esophageal cancer. Cell Mol Life Sci. 2018;75(14):2643-61. doi:10.1007/s00018-018-2757-4
62. Jia KK, Ding H, Yu HW, Dong TJ, Pan Y, Wang Y. Huanglian-Wendan decoction inhibits NF-κB/NLRP3 inflammasome activation in liver and brain of rats exposed to chronic unpredictable mild stress. Mediators Inflamm. 2018;2018:3093516. doi:10.1155/2018/3093516