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Salidroside Improves Hyperuricemia by Simultaneously Regulating Uric Acid Production and Excretion

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Abstract

Background: Hyperuricemia is a common metabolic disease, which seriously affects the quality of life of patients. Salidroside (SAL) is a natural phenolic product extracted from *Rhodiola rosea* root, which is not only less toxic, but also beneficial for metabolic diseases.

Purpose: To investigate SAL's role in regulating hyperuricemia and explore the potential mechanism.

Methods: Molecular simulation was employed to predict the correlation between SAL and TLR4-NLRP3 pathway. The therapeutic effects of SAL were evaluated in cell model and hyperuricemia mice induced by potassium oxonate and hypoxanthine. Then, the mechanism was explored using Western blot assay.

Results: Prediction results showed that SAL bound stably to target proteins TLR4, NLRP3, Caspase-1, and IL-1 β involved in the classical pathway of hyperuricemia TLR4-NLRP3. Further hyperuricemia cell and mice models all showed SAL treatment did decrease the uric acid, creatinine and blood urea nitrogen level. Importantly, pathological observation demonstrated liver and kidney injuries were rescued using HE examination and renal fibrosis ameliorated by Masson staining, which was superior to the positive allopurinol. In terms of mechanism, proteins related to uric acid production (XOD) and excretion (ABCG2, OAT1, OCT1, URAT1 and GLUT9) as well as TLR4-NLRP3 pathway in cell model and hyperuricemia mice were all recovered after SAL administration, which were consistent with the molecular docking prediction.

Conclusion: SAL may serve as a natural small molecule compound for improving hyperuricemia and its associated complications by inhibiting hepatic uric acid production and enhancing renal uric acid excretion. This discovery provides novel insights into hyperuricemia treatment.

Keywords: Salidroside; Hyperuricemia; Inflammation; Xanthine oxidase; TLR4-NLRP3 pathway

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1. Introduction

Hyperuricemia is a metabolic disorder characterized by abnormal production and excretion of uric acid in the bloodstream [1], resulting in an imbalance of purine metabolism and elevated levels of blood uric acid beyond the body's saturation point [2–3]. This can lead to the formation of urate crystals that deposit in

joints or kidneys, causing gout, uric acid nephropathy, cardiovascular disease, and other chronic conditions [4–5].

Uric acid is the end product of purine metabolism in the body [6]. Its primary source is endogenous synthesis, which involves the catabolism of amino acids, small molecular compounds, and nuclear proteins in liver and small intestine tissues. Another part comes from exogenous intake through dietary absorption and metabolism of purines [7–8]. The production of uric acid is a complex process that involves numerous biochemical reactions and enzymes, with xanthine oxidase (XOD) playing a key role in purine degradation to uric acid. XOD can oxidize hypoxanthine or xanthine in the liver to form uric acid [9–10]. However, hyperuricemia leads to an excessive amount of XOD, resulting in depletion of allantoinase and preventing further degradation of uric acid into urea [11]. This abnormal accumulation occurs in patients' serum. Additionally, kidneys play a crucial role in uric acid metabolism within the body. Research has shown that approximately 70% of uric acid metabolism occurs through renal excretion while 30% is broken down via intestinal processes. In terms of kidney excretion, glomeruli filter uric acid from blood into the renal tubule system; most will be reabsorbed back into circulation by renal tubule transporters such as organic anion transporter family (OATs), urate anion transporter family (URATs), adenosine triphosphate binding cassette transporter G2 (ABCG2), and glucose transporter 9 (GLUT9) [12]. However, when blood levels continuously exceed saturation point for uric acid content, it results in accumulation of urate crystals within renal plasma and interstitium regions leading to decreased activity of these transporters along with increased burden on kidneys. Ultimately this can lead to glomerular sclerosis, renal tubule injury, interstitial fibrosis as well as intrarenal inflammatory deposition transforming uric acid [13–14]. Therefore, XOD in the liver and related transporters in the kidney are considered as important targets for the treatment of hyperuricemia.

The latest definitions of asymptomatic hyperuricemia and gout classify them as distinct manifestations of the same underlying disease. The relationship between levels of uric acid accumulation and gout attacks is not linear, and the mechanism by which asymptomatic hyperuricemia leads to gout remains unclear. In gout, the inflammatory response is mediated by a significant number of sodium urate precipitated crystals, typically formed from uric acid, which activate phagocytes, NLRP3 inflammasome, and toll-like receptors (TLR) [12]. However, other studies have found that some gout patients do not exhibit high quantities of sodium urate crystals in their bodies; instead, metabolites from lipid intake or alcohol consumption directly trigger gout attacks by binding to TLR4 and activating the NLRP3 inflammasome. Regardless of the activation pathway involved, the onset of gout is closely associated with the TLR4-NLRP3 inflammatory pathway [15]. When TLR4 detects foreign pathogen molecules such as monosodium urate, it initiates both MyD88-dependent and TRIF-dependent pathways to activate NF- κ B production of inflammatory cytokines like IL-1 β and TNF- α while also activating the NLRP3 inflammasome [16]. Caspase-1 activation results in extensive production of pro-inflammatory cytokines including IL-1 β and IL-18 [17].

Molecular simulation docking technology plays a crucial role in computational biology and drug design as it enables simulation-based prediction of interactions between small molecule compounds and proteins or other biomolecules [18–19]. This technique helps uncover molecular structure-function relationships as well as drug-target interactions [20].

Rhodiola rosea L. (*R. rosea*) is a perennial herb of Chinese Tibetan medicine. It has been widely used in traditional herbal medicine and folk medicine, and listed as a natural plant resource for both medicine and food because of its small toxicity and multiple health benefits [21]. The root of *R. rosea* is its main medicinal part and usually used to prepare herbs, extracts, health products and medicines. Salidroside (SAL, Fig. 1A), a phenolic natural product extracted from *R. rosea*, is one of the main medicinal components [22]. Existing studies show that SAL can effectively improve inflammatory factors such as NLRP3, TLR4, NF- κ B, diabetic nephropathy, inflammatory bowel disease and other diseases, but regulating hyperuricemia is unclear [23–26]. Therefore, this study aimed to study the effects of SAL on hyperuricemia and explore the underlying molecular mechanisms *in vitro* and *in vivo*.

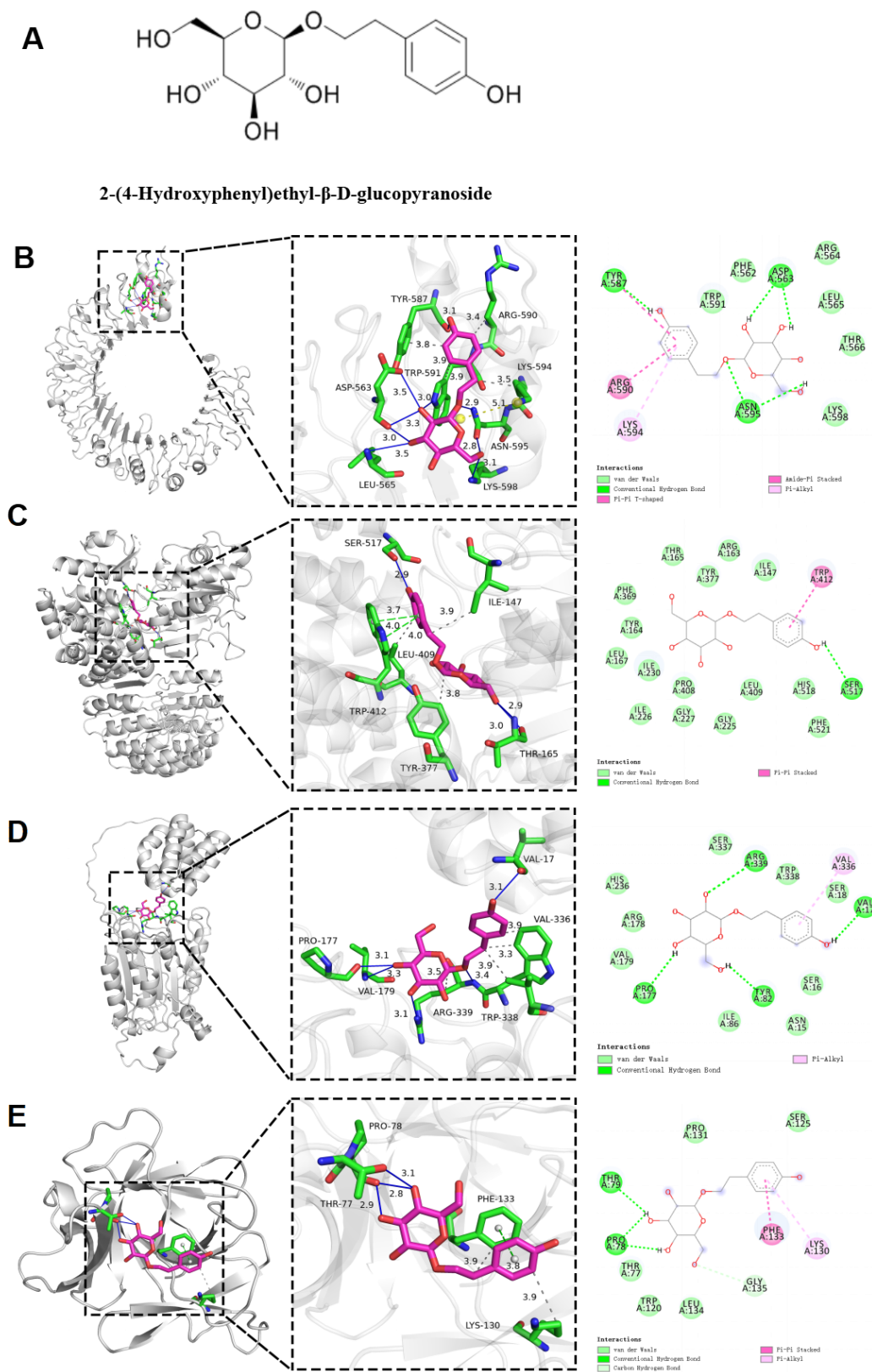


Figure 1. Molecular docking model of SAL binding to target protein. (A) Chemical structure of SAL. (B) SAL and TLR4. (C) SAL and NLRP3. (D) SAL and Caspase-1. (E) SAL and IL-1β. SAL, salidroside.

2. Materials and Methods

2.1. Chemical Agents

Salidroside (SAL, 98% purity, CAS-10338-51-9) was purchased from Shanghai yuanye Bio-Technology Co., Ltd. Xanthine oxidase (XOD, CAS-9002-17-9), uric acid sodium salt (CAS-69-93-2), allopurinol (CAS-315-30-0), *tert*-butylhydroquinone (TBHq), xanthine (CAS-69-89-6) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Potassium oxonate (PO) (01045378) was from Damas-beta (Shanghai, China). Hypoxanthine and benzobromarone (H108384) was purchased from Aladdin (Shanghai, China). Cell counting KIT-8 (CCK-8) was purchased from Solarbio (Beijing, China). XOD, uric acid, SOD (superoxide dismutase) test kits were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

2.2. Molecular Simulation Docking

Chemical structure of SAL was imported into ChemBio3D Ultra 21.0.0.28 for energy minimization, the Minimum RMS Gradient was set to 0.01, and small molecules were saved in pdb format. The optimized small molecule was imported into AutoDocktools (v1.5.6) for hydrogenation, charge calculation and distribution, and the setting of rotatable bonds. Finally, it was saved in "pdbqt" format. The provided protein was imported into Pymol 2.3.0 to remove the protein crystal water, the original ligand, etc., and the protein structure was imported into AutoDocktools (v1.5.6) for hydrogenation, charge calculation and allocation, atom type designation and saving as "pdbqt" format. SAL was docked with TLR4, NLRP3, Caspase-1 and IL-1 β proteins using AutoDock Vina 1.1.2. The interaction pattern was analyzed by using the docking results of PyMOL 2.3.0 and Discovery Studio. Finally, the simulated docking results were screened and analyzed to determine the most likely binding modes.

2.3. Cell Culture

L-O2 cells and RAW264.7 cells purchased from American Type Culture Collection (Manassas, VA, USA) were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin (50 U/mL penicillin and 50 μ g/mL streptomycin) in an atmosphere of 5% CO₂ at 37 °C. HK-2 cells purchased from American Type Culture Collection (Manassas, VA, USA) and cultured in DMEM/F-12 under the same conditions.

2.4. The Effect of SAL on Cell Proliferation Determined by MTT Assay

L-O2 cells, RAW264.7 cells and HK-2 cells were inoculated into 96 wells with a cell density of 1.5×10^4 /well, and the cells grew for 24 h. After 24 h treatment with different concentrations of SAL (1, 5, 10 and 15 μ M), 200 μ L of dimethyl sulfoxide was added to dissolve the remaining MTT formazan crystals for 10 min with shaking. Cell viability was measured at 492 nm using a Flex Station 3 multimode microplate reader.

2.5. Detection of Hyperuricemia Model in L-O2 Cells

Logarithmically growing L-O2 cells were resuspended in DMEM and inoculated into 6-well plates at a density of 3×10^5 cells per well. After 24 h, the supernatant was discarded and the cells were gently washed once with phosphate buffered saline (PBS). Subsequently, serum-free DMEM was used to prepare SAL solutions with different concentrations (1, 5, 10 and 15 μ M), meantime allopurinol (10 μ M) also prepared in serum-free DMEM served as the positive control; each well received a volume of 2 mL. Following treatment for another 24 h, the supernatant from each well was discarded, PBS was used to wash the cells once again, and then an additional volume of 2 mL hypoxanthine solution (800 μ M) prepared without serum in DMEM was added before incubating at 37 °C. After 24 h, xanthine oxidase was added at a concentration of 4 μ L/well (final concentration of 0.3 U/g), incubated for 1 h, and the supernatant was collected for uric acid content; protein was extracted for western blot detection. Experiments were repeated at least three times.

2.6. Detection of Hyperuricemia Model in HK-2 Cells

Logarithmically growing HK-2 cells were resuspended in DMEM/F-12 and inoculated into 6-well plates at a density of 5×10^5 /well. After 24 h, the supernatant was discarded and the cells were gently washed once with PBS. Then SAL was prepared with serum-free DMEM/F-12 at different concentrations (1, 5, 10 and 15 μ M), and benzbromarone (10 μ M, prepared with serum-free DMEM/F-12) as positive control, adding 2 mL per well. The hyperuricemia model was induced by adding urate (final concentration, 8 mg/dL) to each well except the blank group and cultured in the incubator for another 48 h. The content of uric acid in supernatant was detected. The protein was extracted for western blot detection. The experiment was repeated at least three times.

2.7. Cell Viability

HK-2 cells of logarithmic growth stage were re-suspended in DMEM/F-12 and inoculated into 96-well plates at a density of 1×10^4 cells per well. The administration method was the same as above, the final concentration of uric acid was adjusted to 12 mg/dL to induce the apoptosis model of HK-2 cells. After 48 h, 10 μ L CCK-8 reagent was added to each well, and incubated for 1 h. OD values were determined at 450 nm by enzyme-labeler.

2.8. Lipopolysaccharide (LPS)-Induced Inflammation Model in RAW264.7 Cells

RAW264.7 cells were seeded at a density of 1×10^6 cells per plate in 6-well plates. Following pretreatment with LPS (1 μ g/mL) for 1 h using serum-free DMEM, the adherent cells were stimulated with varying concentrations of SAL (5, 10, and 15 μ M) for 24 h. Subsequently, protein extraction was performed for western blot analysis.

2.9. Animals

The SPF grade male ICR mice (20–25 g) in this experiment were purchased from Changzhou Cavens Laboratory Animal Co., Ltd. (Experimental animal use license SU SY21 (Ji13) 217 in 0038). In the breeding and SPF animal room, the temperature was 23 ± 2 °C, with a 12 h light/dark cycle. All animal care and experimental procedures were in compliance with international standards and the provisions on the management of laboratory animal affairs issued by the State Science and Technology Commission. This study was approved by the Animal Care and Use Committee of Yunnan Agricultural University (YUAN2023LLWYH003-8).

2.10. Animal Model

After three days of adaptive feeding, 48 mice were randomly divided into six groups, 6 mice per group (Fig. 2).

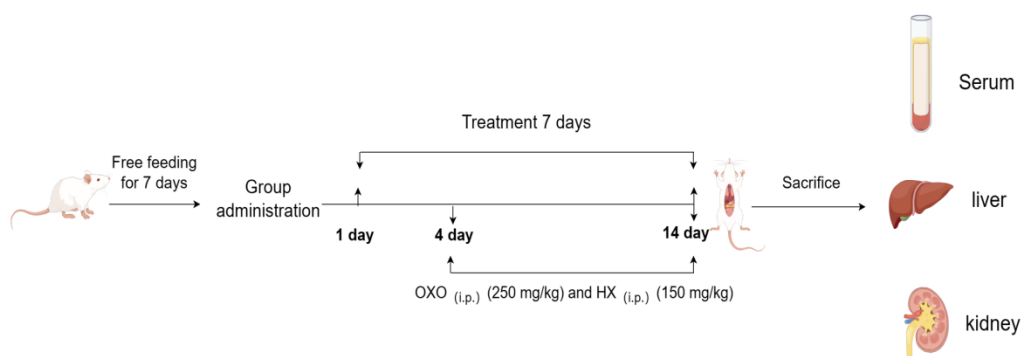


Figure 2. Hyperuricemia animal models and treatment regimens. OXO, potassium oxonate; HX, hypoxanthine; i.p., intraperitoneal injection.

Control group: intraperitoneal injection of normal saline (10 mL/kg) lasted for 14 days.

Model group: Intraperitoneal injection (i.p.) of normal saline (10 mL/kg) lasted for 14 days, and from day 4 to 14, PO (250 mg/kg) and hypoxanthine (150 mg/kg) were injected intraperitoneally to establish the hyperuricemia model.

Allopurinol group: i.p. allopurinol (10 mg/kg) continued for 14 days, and i.p. PO (250 mg/kg) and hypoxanthine (150 mg/kg) from day 4 to day 14.

SAL group: i.p. SAL (20, 40, 80 mg/kg) lasted for 14 days, and i.p. PO (250 mg/kg) and hypoxanthine (150 mg/kg) from day 4 to day 14.

The mice were sacrificed on the 14th day after treatment. Orbital blood and serum were collected to measure XOD activity and biochemical indexes like Serum levels of serum uric acid (SUA), creatinine (CRE), and blood urea nitrogen (BUN). Animal livers and kidneys were preserved for western blot and histopathological analysis.

2.11. Histopathological Evaluation

Liver and kidney tissues were fixed in 4% paraformaldehyde solution, further processed by dehydration, transparency, dewaxing, slicing, dewaxing, hematoxylin-eosin staining or Masson trichrome staining. Pathological morphology of tissues was observed under light microscope [27].

2.12. Western Blot Analysis

Firstly, protein was extracted from cell or tissue homogenates using a high-efficiency RIPA tissue/cell lysate (lysate:PMSF = 100:1) and subsequently quantified by the BCA (bicinchoninic acid) method. The proteins were then separated on a sodium dodecyl sulfate-polyacrylamide gel electrophoresis technique, followed by transfer onto nitrocellulose or polyvinylidene fluoride (PVDF) membranes. The membrane was incubated in 5% BSA at room temperature for 1 hour and subsequently exposed to primary antibody (diluted at 1:1000) overnight at 4 °C. After washing the membrane with TBST (Tris Buffered Saline with Tween® 20) three times, secondary antibody (diluted at 1:5000) was applied. Following incubation, the PVDF membranes were gently shaken and washed with TBST three times for 5 minutes each time at room temperature before capturing images using the FluorChem E system equipped with pro-light HRP chemiluminescence kit.

2.13. Statistical Analysis

Statistical analysis was performed using SPSS 21.0. Data are presented as mean ± SEM. Normally distributed data were analyzed by one-way ANOVA; non-normally distributed data by rank-sum test. Graphs were generated using GraphPad Prism 6. Significance was set at $p < 0.05$ (95% CI).

3. Results

3.1. AutoDock

As depicted in Table 1, the binding energies of SAL with proteins TLR4, NLRP3, Caspase-1, and IL-1 β were lower than $-5 \text{ kcal} \cdot \text{mol}^{-1}$. Notably, SAL formed hydrogen bonds with amino acid residues ASP563, LEU565, TYR578, TRP591, ASN595 and LYS598 of TLR4 receptor protein; established a salt bridge interaction with ARG594 residue; and engaged in hydrophobic bonding interactions with TYR587, ARG590, TRP591, LYS594 residues (Fig. 1B). SAL also formed hydrogen bonds with THR165 and SER517 amino acid residues of NLRP3 receptor protein; participated in hydrophobic bonding interactions involving ILE147, TYR377, LEU409 residues of NLRP3 receptor protein; as well as underwent Pi-stacking interaction with TRP412 residue on this particular receptor (Fig. 1C). Furthermore, SAL interacted via hydrogen bonding interactions specifically targeting VAL17, VAL179, ARG339 amino acid residues on Caspase-1 receptor protein; while engaging in hydrophobic bonding interactions involving VAL336, TRP338, ARG339 residues on Caspase-1 receptor protein (Fig. 1D). Lastly, SAL binds to LYS130 and PHE133 amino acid residues on IL-1 β receptor protein, establishing hydrophobic bonding interactions with

LEU97 and ILE129 amino acid residues on the IL-1 β receptor protein (Fig. 1E). These results show that SAL and these four proteins can be stably bonded through hydrophobic forces, hydrogen bonds, π -stacking forces, and salt bridge forces.

Table 1. Molecular docking of SAL with key TLR4-NLRP3 targets. SAL, salidroside.

Compound	TLR4	NLRP3	Caspase-1	IL-1 β
SAL	-6.8	-7.7	-6.4	-6.4

3.2. Effects of SAL on Cell Proliferation

The MTT experiment results showed that no inhibition was observed on the survivals of L-O2 cells, HK-2, and RAW264.7 at 15 μ M (Fig. 3A, B and C). Therefore, concentrations of 15, 10, and 5 μ M were selected for subsequent experiments.

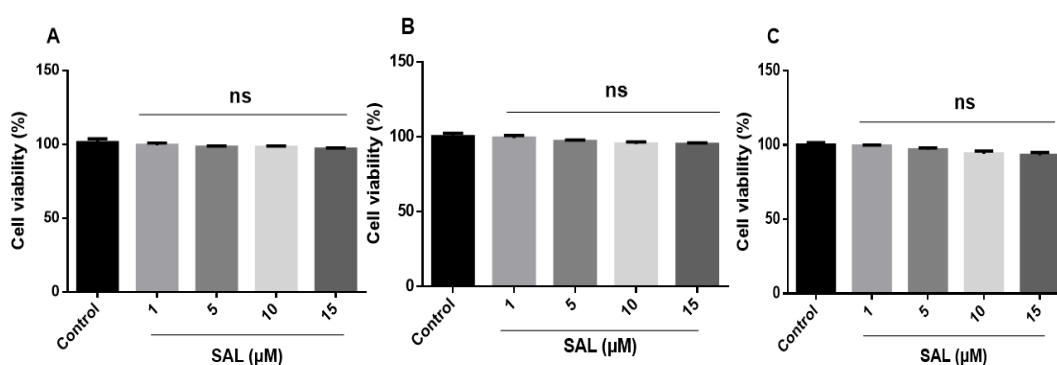


Figure 3. Effects of different concentrations of SAL on cell proliferations. (A) L-O2 cell viabilities. (B) HK-2 cell viabilities. (C) RAW264.7 cell viabilities. These data were analyzed using ANOVA and are presented as mean $\pm$ standard error. Statistic: ns, not significant ($p > 0.05$). SAL, salidroside.

3.3. SAL Inhibited Uric Acid Production in L-O2 Cells Induced by Hypoxanthine and XOD

Based on the study of uric acid synthesis pathway, the combination of hypoxanthine and XOD induced L-O2 liver cells. The findings demonstrated a significant increase in uric acid levels within the model group following combined induction with hypoxanthine and XOD. Importantly, intervention with SAL resulted in a substantial reduction in cellular uric acid levels ($p < 0.05/0.01$, Fig. 4A). Furthermore, compared to the model group, SAL effectively reduced the expression level of XOD (Fig. 4B), a key protein involved in uric acid synthesis. It also decreased the expressions of TLR4, NLRP3, Caspase-1, all key proteins in the TLR4-NLRP3 pathway (Fig. 4C). These findings were consistent with the results predicted by molecular simulation. The above results indicated that SAL had the potential to attenuate uric acid synthesis and modulate the expression of proteins associated with the TLR4-NLRP3 pathway by regulating XOD activity.

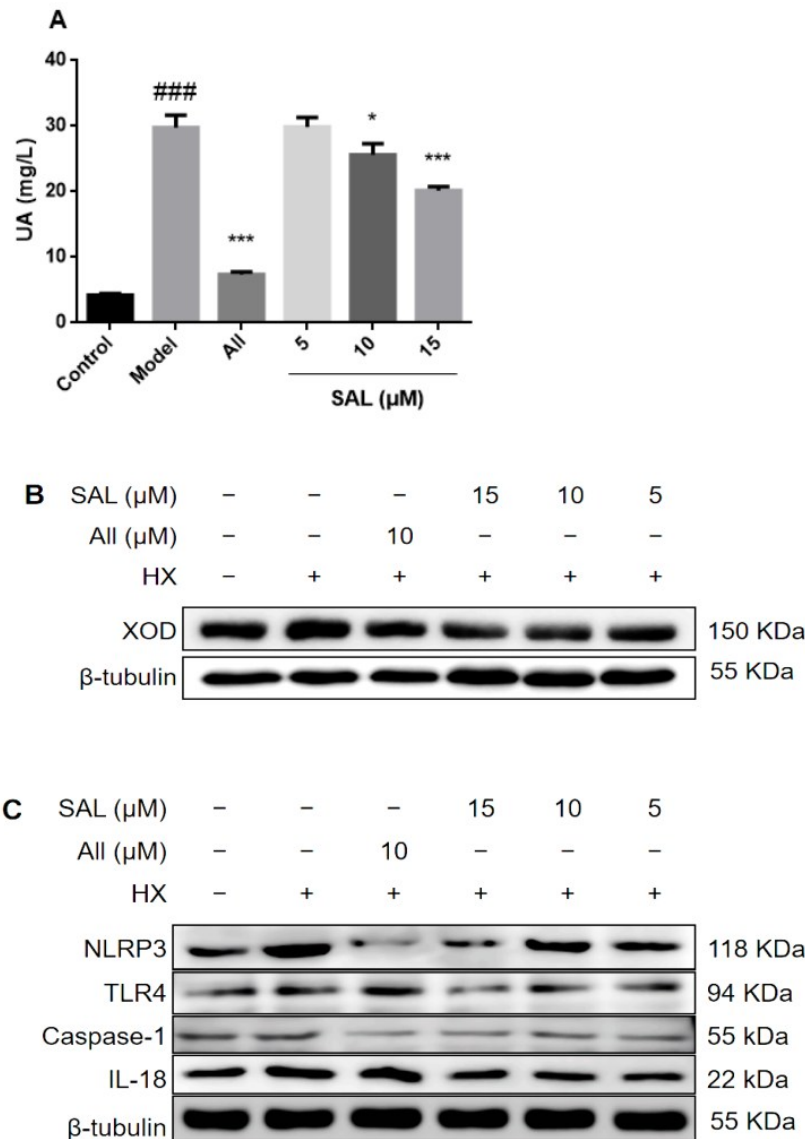


Figure 4. SAL effectively inhibited UA production and protein expressions in L-O2 cells induced by hypoxanthine and XOD. (A) Uric acid levels in the supernatant of L-O2 cells. (B) Protein bands of XOD. (C) Protein bands for NLRP3, TLR4, Caspase-1, IL-18. ANOVA was used to analyze the data, presented as mean $\pm$ SEM. Statistics: ### p < 0.001 versus the Control group; * p < 0.05, ** p < 0.01, *** p < 0.001 versus the Model group. UA, uric acid; All, allopurinol; HX, hypoxanthine; SAL, salidroside.

3.4. SAL Promoted Uric Acid Excretion in HK-2 Cells Induced by Sodium Urate

Based on the excretion pathway of uric acid, this experiment used sodium urate to induce hyperuricemia model in HK-2 cells [28]. The results showed that sodium urate significantly inhibited uric acid excretion, while reversed after SAL intervention (p < 0.05/0.01, Fig. 5A). At the same time, HK-2 cell viabilities presented a reduction after modeling, while SAL can effectively improve cell survival rates and inhibit cell damage (p < 0.05/0.01, Fig. 5B). Additionally, following induction with sodium urate, the expressions of uric acid transporters ABCG2, OAT1, and OAT3 decreased, whereas reabsorption proteins URAT1 and GLUT9 increased. After SAL treatment, there was a significant increase on these transporter proteins, accompanied by a significant inhibition in uric acid reabsorption (Fig. 5C). These results indicated that SAL could regulate the effect of uric acid on renal cells.

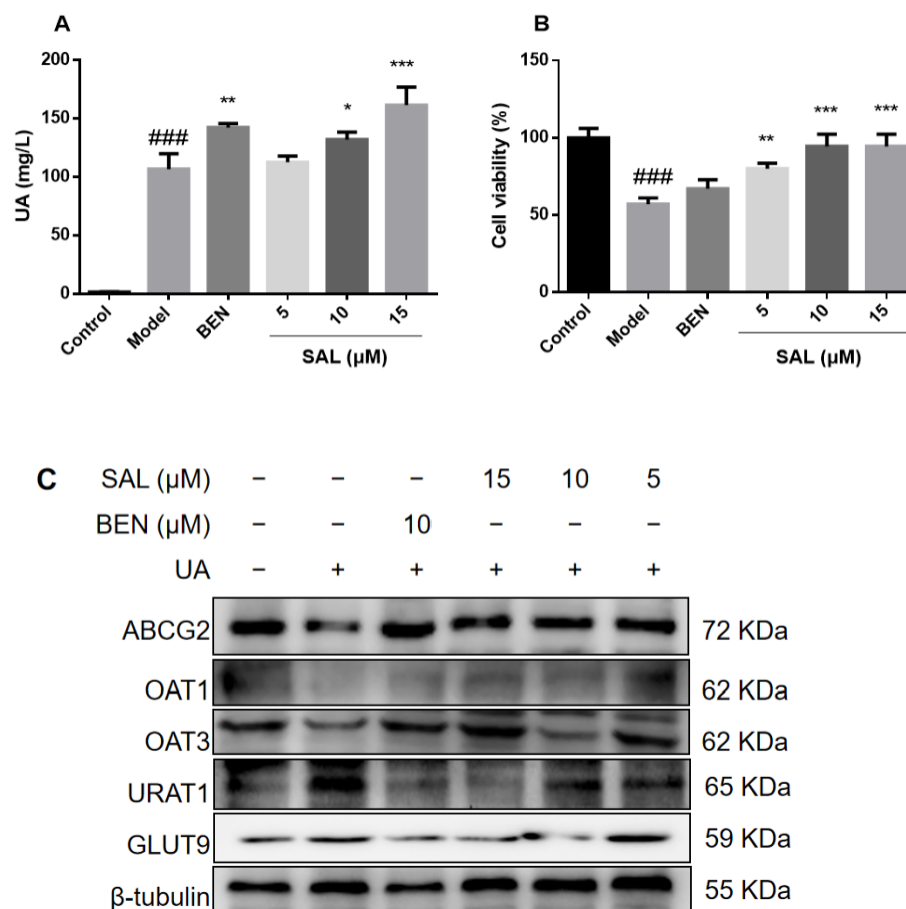


Figure 5. SAL effectively promoted the excretion of uric acid in HK-2 cells induced by sodium urate. (A) Uric acid levels in the supernatant of HK-2 cells. (B) Survival rates of UA-induced HK-2 cells. (C) Protein bands for ABCG2, OAT1, OAT3, URAT1, GLUT9. ANOVA was used to analyze the data, presented as mean $\pm$ SEM. Statistics: ### p < 0.001 versus the Control group; * p < 0.05, ** p < 0.01, *** p < 0.001 versus the Model group. UA, uric acid; All, allopurinol; BEN, benzbromarone; SAL, salidroside.

3.5. SAL Attenuated LPS-Induced Inflammation in RAW264.7 Cells

Based on the findings of hyperuricemia in L-O2 cells, we utilized LPS-induced inflammation in RAW264.7 cells to further elucidate the role of SAL in modulating the TLR4-NLRP3 inflammatory pathway. The results demonstrated (Fig. 6) an upregulation of key proteins within the TLR4-NLRP3 pathway in RAW264.7 cells upon LPS induction, whereas intervention with SAL significantly attenuated the expression levels of TLR4, NLRP3.

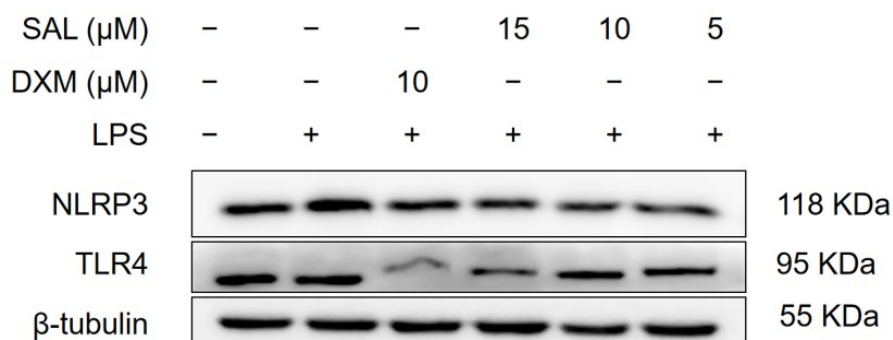


Figure 6. The administration of SAL attenuated LPS-induced inflammation in RAW264.7 cells. These data were from three independent experiments presented. SAL, salidroside; DXM, dexamethasone; LPS, lipopolysaccharide.

3.6. SAL Alleviated Weight Loss in Hyperuricemia Mice

Fig. 7A demonstrated that, in comparison to the control group, mice in the model group exhibited a significant weight loss from day 4 to 14 after induction. In contrast to the model group, administration with SAL significantly increased the weight of mice, particularly the high dose group exhibiting the most pronounced remission effect. Consequently, SAL effectively mitigated hyperuricemia-induced weight decreases in mice.

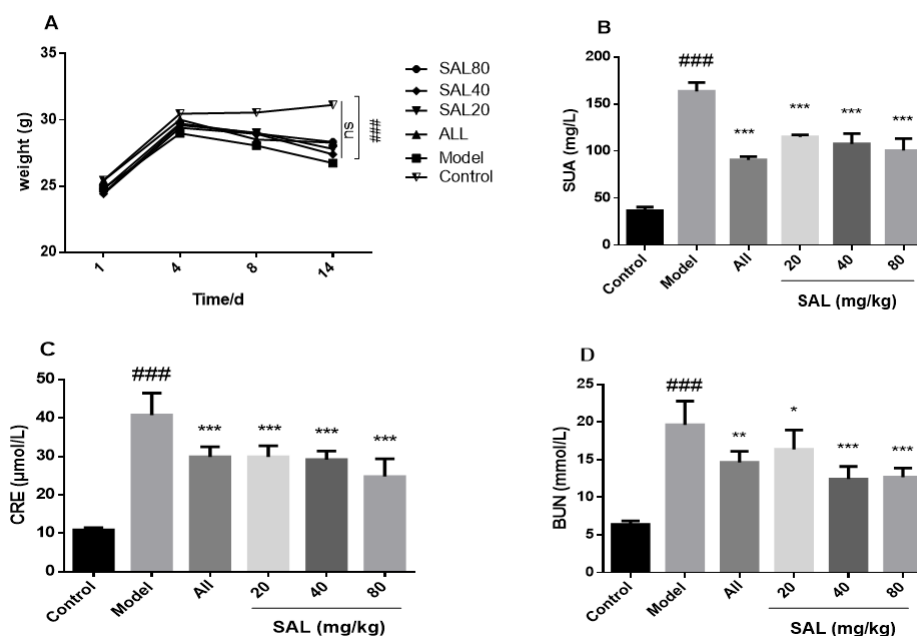


Figure 7. Effects of SAL on body weight, SUA, BUN and CRE in hyperuricemia mice. (A) Weight level; (B) SUA level; (C) CRE level; (D) BUN level. Data that conform to a normal distribution are reported as mean $\pm$ standard error of the mean (SEM), whereas data with a non-normal distribution are reported as median and interquartile range [M (Q1–Q3)]. $n = 6$ per group. Statistics: ### $p < 0.001$ versus the Control group; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ versus the Model group; ns, not significant ($p > 0.05$). SAL, salidroside; SUA, serum uric acid; CRE, creatinine; BUN, blood urea nitrogen.

3.7. Effects of SAL on Serum Biochemical Parameters in Hyperuricemia Mice

Serum levels of serum uric acid (SUA), creatinine (CRE), and blood urea nitrogen (BUN) are crucial biochemical markers for evaluating hyperuricemia and renal function. The results (Fig. 7B, 7C and 7D) demonstrated a significant increase in SUA, CRE, and BUN in the model group compared to the control

group ($p < 0.001$). Conversely, treatment with SAL resulted in a significant reduction in these marker levels when compared to the model group ($p < 0.05/0.001$). Notably, the positive control group exhibited a significant decrease only in SUA, no substantial decrease was observed in CRE and BUN levels ($p > 0.05$). These findings indicated that SAL effectively reduces SUA levels and protects kidney function.

3.8. Effects of SAL on Serum XOD and Superoxide Dismutase (SOD)

The XOD and SOD are two key enzyme indicators used to assess uric acid production capacity and antioxidant capacity. Fig. 8 results showed that, compared with the control group, the serum XOD activity in the model group significantly increased ($p < 0.001$, Fig. 8A), while the SOD level significantly decreased ($p < 0.001$, Fig. 8B). Both the SAL administration group and positive control effectively reduced serum XOD activities and increased SOD compared to the model group ($p < 0.05/0.01/0.001$). These findings indicated that SAL could alleviate uric acid level elevation and oxidative stress in hyperuricemia mice by decreasing serum XOD activities and increasing SOD.

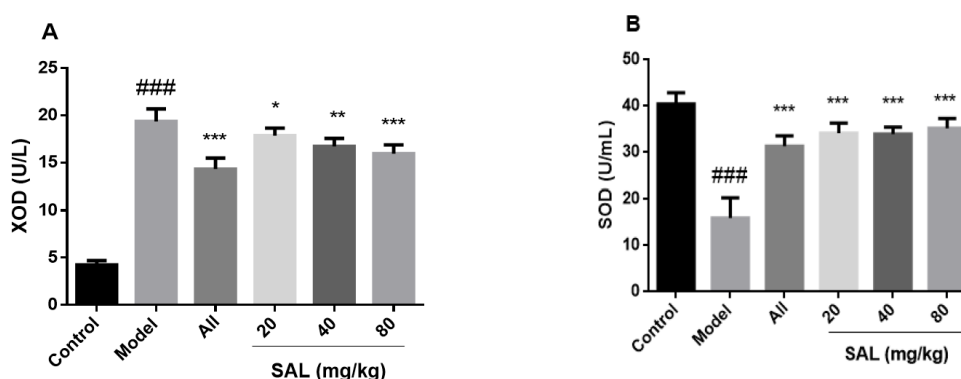


Figure 8. Effects of SAL on serum XOD and SOD in hyperuricemia mice. (A) Serum XOD level. (B) Serum SOD level. ANOVA was used to analyze the data, presented as mean $\pm$ SEM ($n = 6$). Statistics: ### $p < 0.001$ versus the Control group; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus the Model group. SAL, salidroside; SOD, superoxide dismutase.

3.9. Effect of SAL on Histopathological Damage of Liver and Kidney

HE staining showed (Fig. 9A) that the liver cells in the control group were uniform in size and shape. In the model group, occasional spotty necrosis of hepatocytes, nucleolysis, homoplasmic red staining, and small focal infiltration of lymphocytes and granulocytes were observed around the portal area of liver tissue. Circular microvesicles could be seen in the cytoplasm of hepatocytes; a few veins appeared as bruising, but there was no significant dilation or compression of hepatic sinuses. Compared with model group, liver tissue injury was reduced in positive control group, but spot-like necrosis of hepatocytes was occasionally observed around the sink area, accompanied by small focal infiltration of lymphocytes and granulocytes. Circular microvesicles were occasionally observed in the cytoplasm of hepatocytes. No significant abnormalities were observed in mouse liver tissues from medium- and high-dose SAL administration groups compared to simulated groups except for occasional cell particle degeneration. Cytoplasmic porosity and eosinophilic particles occurred occasionally within low-dose SAL-administered mice's liver tissues as well as round microvesicles within their cytoplasm. These results suggested that SAL had protective effects on hyperuricemia-induced liver injury.

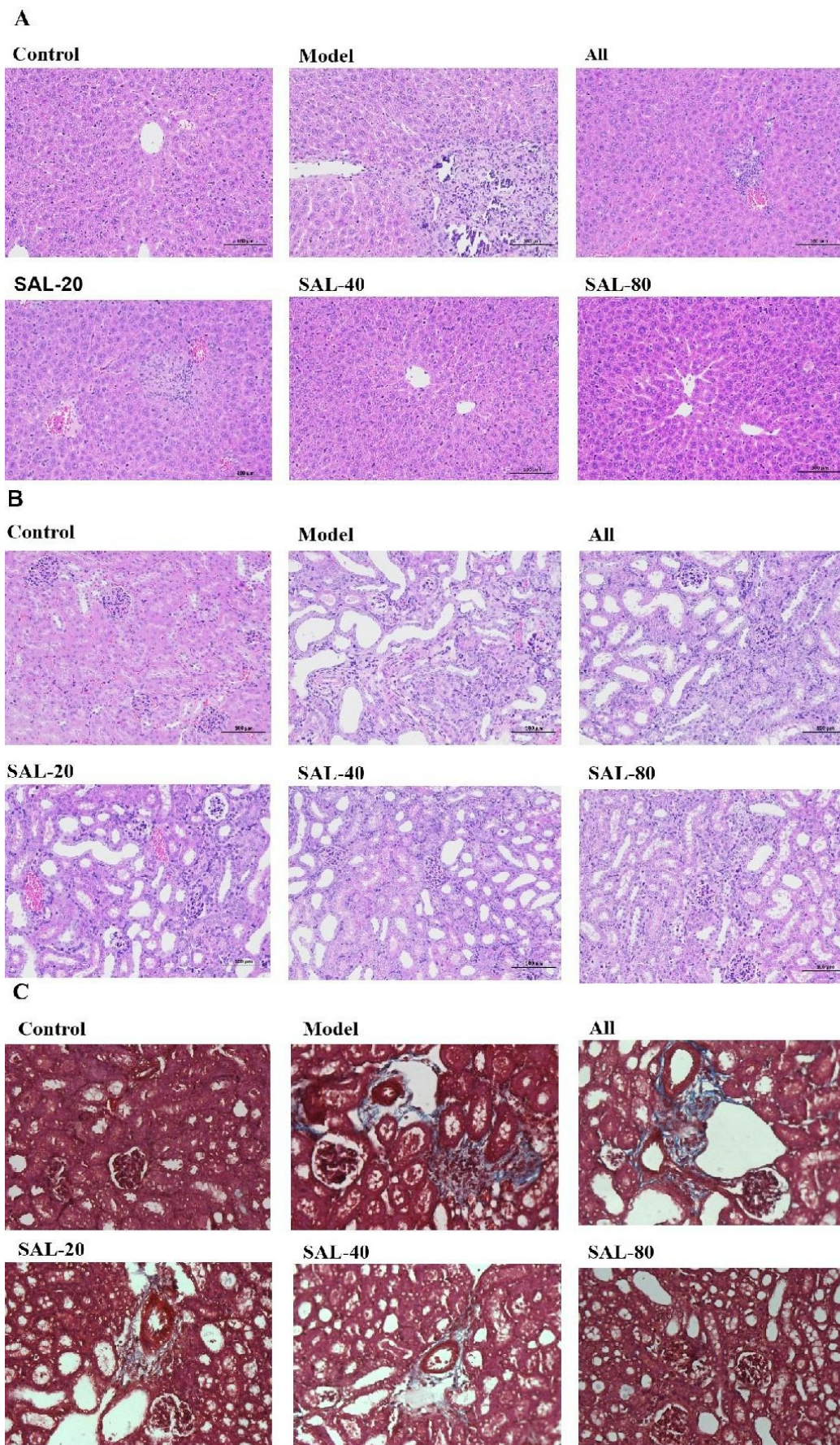


Figure 9. SAL has a protective effect on histopathological damage of liver and kidney in hyperuricemia mice. (A) The provided image displays liver tissue stained with H&E at a magnification of $\times 400$ (scale = 100 μm). (B) The provided image displays kidney tissue stained with H&E at a magnification of $\times 400$ (scale = 100 μm). (C) The provided image displays kidney tissue stained with Masson at a magnification of $\times 400$.

The results of renal HE staining (Fig. 9B) showed that the kidney tissue of mice in the control group was normal, and no necrosis or inflammatory cell infiltration was observed. Compared to the control group, the kidney tissue of mice in the model group exhibited a large number of renal tubule atrophy, lumen stenosis, weakened cytoplasmic eosinophilic acid, large renal tubule dilation, irregular lumen shape, flat epithelium, more degeneration particles in renal tubule epithelium, loose and lightly stained cytoplasm, as well as mild connective tissue hyperplasia. Occasional annular infiltration of lymphocytes around blood vessels can be seen. In comparison to the model group, kidney tissue from mice in the positive control group still showed a large number of renal tubule atrophy, a large number of dilated renal tubules, irregular lumen shape, flat epithelium occasionally accompanied by perivascular edema and loosely arranged connective tissue. Compared to the model group, high-dose SAL treatment significantly reduced kidney injury with only a small number of cases showing renal tubule atrophy, lumen stenosis, weakened cytoplasmic eosinophilic acid levels, and a small number exhibiting dilated renal tubules.

Kidney Masson staining demonstrated (Fig. 9C) that, compared to the control group, the model group exhibited prominent blue staining in glomeruli and renal tubules, along with excessive collagen deposition and evident fibrosis. Treatment with varying doses of SAL significantly ameliorated collagen deposition and fibrosis.

3.10. SAL Inhibited XOD Expression of Liver and Down-Regulated TLR4-NLRP3 Pathway

The above study had demonstrated that SAL could regulate XOD activity in L-O2 cells, thereby reducing uric acid synthesis, and down-regulate the expression of TLR4-NLRP3 pathway-related proteins. Based on these findings, we investigated relevant proteins of liver tissues on hyperuricemia mice. The results revealed (Fig. 10A and 10B) a significant increase in XOD, TLR4, NLRP3, Caspase-1, TNF- α and IL-18 expressions in model group compared to the control group. Expectedly, following 14 days of SAL intervention, there was a remarkable inhibition on these proteins, among which, high-dose group presented the most pronounced effects. These results indicated that SAL could effectively suppress uric acid production by regulating XOD activity and inhibiting TLR4-NLRP3 pathway-related proteins in hyperuricemia mice, consistent with observations in cell models.

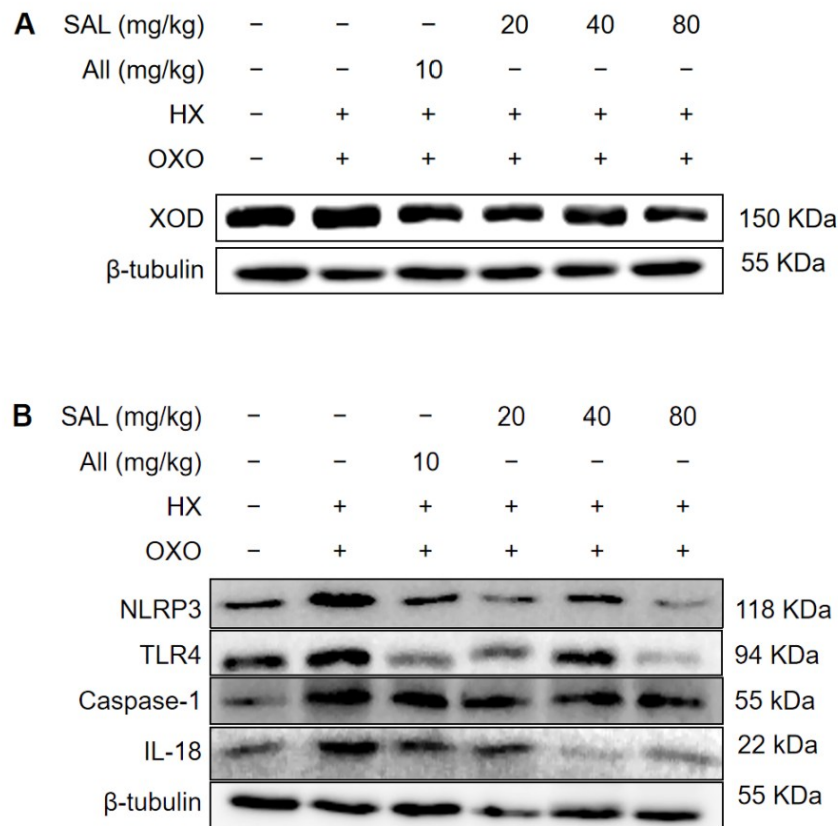


Figure 10. SAL effectively inhibited XOD protein of livers in hyperuricemia mice, and down-regulated TLR4-NLRP3 pathway-related proteins. (A) XOD protein band. (B) NLRP3, TLR4, Caspase-1, IL-18. These data were from three independent experiments presented.

3.11. SAL Regulated Renal Tissue-Associated Uric Acid Transporters

Compared with the control group (Fig. 11), model group kidneys showed a decrease in uric acid transporters including ABCG2, OAT1, OAT3, and OCT1. Additionally, there was an increase in uric acid reabsorption proteins URAT1 and GLUT9. Notably, the above four uric acid transporters were significantly increased while the reabsorption proteins inhibited. These findings suggested that SAL could enhance renal uric acid excretion by promoting the expression of uric acid transporters and inhibiting reabsorption proteins. This was consistent with the results observed in the HK-2 cell hyperuricemia model.

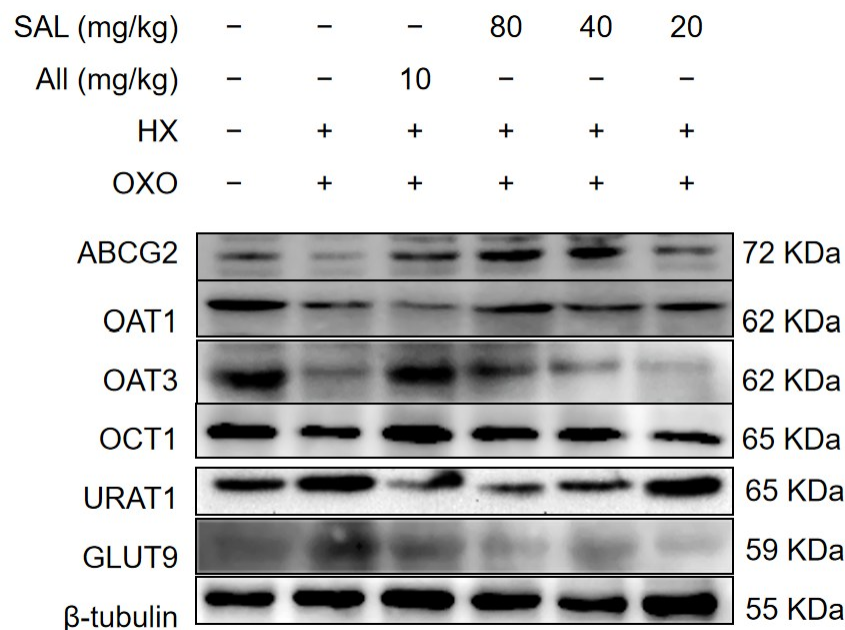


Figure 11. SAL effectively regulated renal tissue-associated uric acid transporters. Western blot for ABCG2, OAT1, OAT3, OCT1, URAT1, GLUT9. These data were from three independent experiments presented.

4. Discussion

The management of hyperuricemia, a metabolic disorder that significantly impacts patients' quality of life, has long been a prominent area of research [29]. However, conventional uric acid-regulating medications such as allopurinol, febuxostat, and benzbromarone primarily lower uric acid levels by directly inhibiting XOD or impeding renal tubular reabsorption of uric acid [30]. Meantime, these drugs impose cardiovascular and cerebrovascular burdens on patients while also affecting liver and kidney functions [31]. Consequently, there is an urgent need to identify natural compounds with high efficacy and low toxicity as a therapeutic approach for hyperuricemia. Salidroside, derived from the root of *R. rosea* as a natural phenolic product, not only exhibits minimal toxicity and numerous health benefits but also demonstrates promising pharmacological activity in treating metabolic disorders, immune diseases, and oxidative stress.

In this study, the molecular simulation docking was used to predict the binding mode, affinity, and stability of SAL to target proteins related to the TLR4-NLRP3 pathway, which is a classical pathway of hyperuricemia [32–33]. Results showed that the binding energies of SAL with receptor proteins TLR4, NLRP3, Caspase-1, and IL-1 β were all less than -5 . SAL formed stable bonds with these four proteins through hydrophobic forces, hydrogen bonds, π -stacking forces, and salt bridge forces. Then we used hypoxanthine and XOD to induce L-O2 cells to mimic hyperuricemia model of liver cells, and sodium urate to kidney cells HK-2. After SAL intervention, we observed that 15 μ M SAL significantly inhibited uric acid production in L-O2 and promoted uric acid excretion in HK-2. Therefore, it was speculated that SAL could simultaneously treat hyperuricemia by inhibiting uric acid production and promoting its excretion. To verify this hypothesis, Western Blot experiments were performed on both the L-O2 hyperuricemia model and HK-2. Based on previous molecular docking prediction results, target proteins related to the TLR4-NLRP3 pathway were selected for verification. Results on L-O2 cells demonstrated that SAL effectively down-regulated XOD protein and TLR4-NLRP3-related proteins (TLR4, NLRP3, Caspase-1), which was consistent with previous prediction. In kidney cells, SAL significantly promoted the expression of uric acid transporters ABCG2, OAT1 and OAT3; meanwhile, inhibiting reabsorption proteins URAT1 and GLUT9. These findings collectively indicated that SAL could simultaneously treat hyperuricemia by inhibiting uric acid production and promoting its excretion. Currently available drugs for reducing uric acid

levels mainly act through a single pathway and often have significant toxic side effects; therefore, SAL represents a small molecule compound with great potential for treating hyperuricemia.

To further verify the effect of SAL in regulating hyperuricemia, we used PO combined with hypoxanthine to construct a mouse model of hyperuricemia. Previous studies have shown that chronically elevated serum uric acid levels in mice lead to weight loss and liver and kidney damage, characterized by dysregulation of serum XOD, SOD, CRE, and BUN levels [34–35]. Therefore, we recorded changes in the mice's weight and serum biochemical indicators; assessed histopathological injury of tissues; and detected the expression of related pathway proteins in livers and kidneys. Consistently, we found that the serum uric acid of model group increased significantly, while body weights decreased. However, SAL intervention significantly alleviated this situation. In terms of liver injury observation, we found a significant increase in mice serum XOD levels and a significant decrease in SOD in the model group. This indicated an increased burden on liver uric acid production and weakened antioxidant capacity. HE staining revealed obvious liver injury including punctate necrosis of hepatocytes accompanied by small focal infiltration of lymphocytes and granulocytes. Round microvesicles were observed in hepatocyte cytoplasm, along with some visible bruising veins. Compared to the model group, both serum XOD and SOD levels were significantly recovered in the SAL group. Additionally, liver tissue showed no significant abnormalities. This indicated that SAL could effectively protect against liver damage induced by hyperuricemia while inhibiting liver uric acid production. In the observation of kidney injury, we observed significant disorder in CRE and BUN levels in model mice serum. Renal sections exhibited evident tubular atrophy or edematous dilation, irregular luminal shape, extensive degeneration of tubular epithelial cells, and occasional perivascular lymphocytic infiltration. Excessive deposition of collagen around glomeruli and renal tubules led to pronounced fibrosis. After SAL intervention, there was a significant alleviation in CRE and BUN as well as glomerular and renal tubule injury. Interestingly, SAL showed a better protective effect on kidneys compared to allopurinol, a positive control drug. Allopurinol is essentially a purine analogue used clinically for lowering uric acid levels by inhibiting XOD activity and reducing uric acid production rate. However, allopurinol is metabolized into oxypurinol by the kidneys and highly depends on kidney function. Long-term use of allopurinol can increase burden on the kidneys [36].

In order to better explore the mechanism of SAL on hyperuricemia, western blot experiments were performed on liver and kidney tissues of mice. Pleasantly, the related proteins of mice livers and kidneys were consistent with the results obtained in previous cell model. Liver tissues' XOD, TLR4, NLRP3, Caspase-1 and IL-18 proteins, kidneys' uric acid reabsorption proteins URAT1 and GLUT9 were significantly decreased after SAL intervention. However, uric acid transporters ABCG2, OAT1, OAT3 and OCT1 increased. These results once again confirmed that SAL could effectively regulate hyperuricemia by regulating XOD activity, inhibiting TLR4-NLRP3 pathway-related protein expression to inhibit uric acid production, and promoting renal excretion by increasing uric acid transporter expressions and inhibiting reabsorption proteins.

Existing studies have shown that TLR4 is one of the most important pathogen recognition receptors in the body [37]. When serum uric acid remains high for an extended period, TLR4 signaling is activated, and MyD88 protein mediates the activation of nuclear transcription factor NF- κ B, subsequently releasing pro-inflammatory cytokines TNF- α and IL-1 β [38]. Simultaneously, ATP and deoxyuridylate released after TLR4 activation activate NLRP3 signaling within cells, leading to ASC and Caspase-1 activation, ultimately triggering excessive production of pro-inflammatory cytokines such as IL-1 β and IL-18 [39]. This series of reactions results in increased inflammation in the body and eventually leads to diseases like gout and uric acid nephropathy. In summary, it was speculated that SAL's protective effect on liver and kidney injury caused by hyperuricemia also involved inhibiting the TLR4-NLRP3 pathway, a core pathway regulating hyperuricemia. Although SAL may not perform as well as allopurinol in simply lowering uric acid levels, we believed that SAL had potential as a low-toxicity drug for treating hyperuricemia due to its multiple pathways involvement and long-term use benefits. However, further studies were needed to analyze its potential therapeutic mechanisms and effects to provide a more reliable basis for clinical application.

5. Conclusions

Collectively, this study found that SAL is a natural small molecule compound that can improve hyperuricemia and its complications by inhibiting liver uric acid production and promoting renal uric acid excretion. This provides new clues for the treatment of hyperuricemia.

Author Contributions

Writing – original draft, Writing – review & editing: S.-S.Z.; Funding acquisition, Supervision, Project administration: J.S., Y.-L.Z., X.-J.W.; Methodology, Conceptualization: S.-D.L., D.C., M.-Y.W., M.-F.A., S.-J.F., T.-T.J.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Statement

All animal care and experimental procedures were in compliance with international standards and the provisions on the management of laboratory animal affairs issued by the State Science and Technology Commission. This study was approved by the Animal Care and Use Committee of Yunnan Agricultural University (YUAN2023LLWYH003-8).

Data Availability

The data that support the findings of this study are available from the corresponding authors and first author upon reasonable request.

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